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THE PHYSIOLOGICAL ACTIVATION OF INSULIN *

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WHILE the most striking effects of insulin are seen in the disease diabetes mellitus the current conceptions of its action are based, almost exclusively, on data obtained from healthy human beings or experimentally prepared, but otherwise normal, animals. It is not, therefore, surprising that discrepancies have arisen between physiological conclusions and medical observations, but it is unfortunate that these discrepancies have been solved by relative neglect of the clinical findings. The result has been that many well established observations on insulin action in diabetes have failed to influence physiological thought to the extent that their actual significance would appear to justify.

One of the earliest of such independent observations by the clinician was that of the variation of insulin efficiency under the influence of various factors. It was speedily recognised that infection in the diabetic necessitated the temporary administration of larger doses of insulin, that in cases of diabetic coma hundreds of units of insulin may be required to influence the blood sugar level, whilst in the same patients, after emergence from coma, twenty or thirty units result in marked hypoglycæmia, that if a diabetic be given three meals of identical composition in the day more insulin is required to prevent glycosuria after the morning meal than after either of the others and that cases are met with in which resistance develops to the action of insulin, even when given in enormous doses. It is a more recent finding that the composition of the diet has a marked influence upon the capacity of the diabetic to dispose of sugar. Cases of diabetes have been under our care in which, by decreasing the fat and increasing the carbohydrate in the diet, less insulin was required to keep the urine sugar free on the high carbohydrate than on the high fat regime. In these cases it is difficult to avoid the conclusion that the insulin has become more efficient and it was decided to investigate whether this potentiation was real or only apparent. Owing to the slower succession of events in the diabetic than in healthy individuals undergoing the same tests, phenomena

* A preliminary account of this work appeared in the *Lancet*, 1932, ii, 935

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became obvious in the former which were only later detected in the normal after careful search. As these phenomena occurred both in the abnormal and normal individuals, it was thought necessary to investigate them more closely in the healthy person and to define their limits of normality, before proceeding further with the investigation of the diabetic. It is these observations on the normal which are presented below. In order to make clear the scheme of attack on the problems investigated it is necessary first to consider some theoretical considerations underlying the tests used.

The peripheral action of insulin was clearly demonstrated by the experiments of Mann and Magath (22) and Burn and Dale (5). The former investigators showed that, after hepatectomy in dogs, insulin produced a fall in blood sugar comparable with that obtained in the normal animal, whilst the latter observers demonstrated the disappearance of large quantities of infused sugar in their decapitated eviscerated preparations after administration of insulin. These findings threw considerable light upon the earlier results of Foster (9) who had shown that in man, venous blood contained less sugar than capillary blood. Correlation was further established in experiments on dogs by Frank, Nothmann and Wagner (10a, 10b) who showed that injection of insulin, both in the intact and in the depancreatized animal caused an increase in the arteriovenous sugar difference, and moreover that this A-V difference, after intra-arterial injection of insulin, was most marked in the limb supplied by that artery. These workers also reported that an A-V difference normally existed under resting conditions in intact dogs but that it was undetectable in depancreatized animals. A diminished A-V difference in diabetics and its increase under the action of insulin were recorded by Lundsgaard and Holboll (21), and these observations have since been confirmed by other investigators (20) (26).

The following points thus appear to be proved. That insulin has an action in the peripheral tissues, that this action is revealed by the A-V difference in the blood sugar, that increasing the insulin in the tissues results in an increase in the A-V difference, and that restriction of this substance in the body, by pancreatectomy and possibly by disease, causes a decrease and in some cases a disappearance of this phenomenon. There are, therefore, strong grounds for believing that the A-V difference depends upon the amount, or the concentration, of active insulin in the tissues.

Foster (9) established the important point that, during hyperglycaemia induced by ingestion of glucose, the A-V difference rapidly increased after the first few minutes so that the venous curve remained much lower than the capillary blood sugar curve. These results have been confirmed by Cori and Cori (6) and numerous investigators since. It appears, therefore, that hyperglycaemia occasions an increase in the active insulin in the tissues. This deduction is further supported by the experiments of Zunz and la Barre (33) and Grafe and Meythaler (12) who bring forward results showing that a rise in blood sugar is an adequate stimulus for the secretion of insulin from the pancreas.

Consequently the fundamental assumption for interpretation of the arterio-venous blood sugar curves in the following series of experiments is *that the difference between the sugar content of arterial and venous blood, at any particular time, is an indication of the active insulin then present in the tissues*

Course of investigation

It was noted in diabetics balanced on a high fat diet, that if the amount of carbohydrate were trebled or quadrupled, and the amount of fat reduced so that the caloric value of the diet was the same, then, despite the increased carbohydrate intake, the same insulin still sufficed to keep the urine sugar free. This paradoxical variation in insulin efficiency was found to be accompanied in these patients, when on a high carbohydrate diet, by a less degree of hyperglycaemia after a standard dose of glucose, than in the same patients when receiving a high fat diet.

Du Vigneard and Karr (8) reported that the sugar tolerance in rabbits was markedly decreased by fasting or by a diet containing a large proportion of fat, whilst a diet containing much carbohydrate increased the sugar tolerance. That these variations in tolerance were not due to variations in absorption was shown by du Vigneard and Karr (8) when they demonstrated that the same type of hyperglycaemia occurred whether the sugar was given orally or intravenously. Observations of a similar nature were recorded from time to time and Sweeney (30) reported the influence of starvation, high fat and high carbohydrate diets on the sugar tolerance of healthy human beings. He found that after a standard dose of glucose a high blood sugar curve invariably occurred in subjects who were either starving or on a high fat diet whilst a low blood sugar curve accompanied a high carbohydrate regime. The present investigation was undertaken in an attempt to explain this influence of diet on the sugar tolerance, but evidence rapidly accumulated which indicated that this problem was primarily concerned with the effect of these factors upon the activity of insulin. This development of the original problem proceeded along the following lines of argument.

As far as we know hyperglycaemia in a healthy individual can be reduced in one of two ways. The blood sugar can either be stored in the liver or removed at the periphery. The first point to be decided was, therefore, is the lower blood sugar curve, accompanying the high carbohydrate diet, due to increased peripheral removal or increased hepatic storage? The more sugar removed in the peripheral circulation, the greater will be the difference between the sugar content of arterial and venous blood, so that the construction of simultaneous arterial and venous blood sugar curves might be expected to provide data for localising the site of abstraction. We have given above our reasons for thinking that the A-V difference is a measure of the active insulin in the tissues, and thus the A-V curves also provide data for answering another question, namely, is the low curve found on the high carbohydrate diet due to increased peripheral action of insulin?

If this is found to be so then a third question presents itself with three possibilities. Is the increased peripheral action of insulin due to increased supply, or to increased activity of endogenous insulin, or to removal of some substance inhibiting insulin action? The first possibility can be examined by studying the activity of injected insulin. If this is found to be increased on the high carbohydrate diet, as measured by the rate of depression of the blood sugar, then the decision must be between the last two possibilities. This difficult point at present, admits of no direct solution but circumstantial evidence will be seen to suggest the conclusion that insulin both as injected, and as secreted by the pancreas, is normally activated in the body by some unknown substance.

The problems stated above have been investigated by two methods. Under each set of experimental diets, high fat and high carbohydrate respectively, detailed curves have been made of the blood sugar contents of capillary and venous blood after administration of glucose, and under the same dietary conditions the rate and degree of depression of the capillary blood sugar, after intravenous injection of a standard dose of crystalline insulin, has been measured. These curves will be referred to respectively as the "arterio-venous" curves (A-V curves) and the "insulin depression" curves.

Methods

Healthy young men, ranging in age from 18 to 22, were used for the investigation. As far as could be ascertained none had a family history of diabetes mellitus, none had suffered from any serious illness, and at the time of investigation neither signs nor symptoms of disease were present in any of them. For the reasons given below, they were selected with special reference to the anatomical arrangement of the veins in their anti-cubital fossæ and the shape of the lobes of their ears.

The subject was admitted to the ordinary ward and placed on the diet prescribed. Strict confinement to hospital was not insisted upon, ordinary activities were permitted, but vigorous exercise was forbidden. Despite this there is no reason to think that any of the subjects supplemented their diet. This could, to some extent, be checked as on the most irksome diet, that containing much fat, ingestion of carbohydrate was speedily revealed by diminution of ketonuria.

Each meal was weighed, prepared and checked in the special Diet Kitchen of the hospital*. If, on any occasion, the full amount of food was not eaten the matter was reported and a note made to that effect. The diet was divided into three main meals of equivalent composition which were eaten at 6 a.m., 12 p.m. and 6.30 p.m. and a lighter meal containing the same proportion of the three foodstuffs which was given at 3.30 p.m. The actual composition of the diet for any experiment is given in terms of carbohydrate, protein and fat at the bottom of each figure. It should be noted that the amount of protein in each type of diet was always kept constant, and that

the subject was allowed at least five days in which to become adjusted to any particular diet before any experiment was performed

Before any test the last meal was taken at 6 30 p m the previous night, but water was allowed freely, save during the four hours prior to the investigation. All experiments, unless otherwise stated, were performed at 10 a m. In the sugar tolerance tests 50 g of glucose, flavoured with a little essence of lemon, were given by mouth in 300 c c of water and blood samples were taken both in capillary and venous blood. In the insulin depression curves insulin solution was injected into the same point of the same vein for each test and capillary blood samples only were obtained.

As the sugar content of the blood in either the capillaries or the veins can be influenced by changes in the circulation rate to the part, every effort was made to exclude stimuli liable to initiate vasomotor reflexes. Muscular action and changes in temperature of the environment are potent factors in producing such a redistribution of the circulation and precautions were accordingly taken against these sources of error. The patient remained in bed until half an hour before the experiment was due to begin. He was then brought into the laboratory, near the ward, and seated in a comfortable chair. In this he remained until the end of the investigation and during that time the minimum of movement was allowed. The effects of changes in temperature were guarded against by maintaining the room steady at 20° C by shielding the patient from draughts, and by protecting the exposed parts other than the face, with light coverings. By appropriate adjustments of clothing it was ensured that the patient did not feel either too warm or too cold. Any effect resulting from the different temperature of the ward and the laboratory was permitted to subside by allowing the preliminary period of rest. Before beginning any experiment it was ascertained that the ear of the subject was warm to the touch.

Venous blood was obtained from the veins in the antecubital fossa, at 6 to 10 minute and later 15 minute intervals. In each subject every specimen of blood was withdrawn from the same half inch of vein in every experiment. Comparison is thus possible between the different curves on any one subject. The vein selected was the one that appeared to carry the most blood from the deep tissues. An all-glass syringe of 1 c c capacity and a fine hypodermic needle were used. The syringe was prepared by putting a knife point of powdered potassium oxalate in the barrel and greasing the plunger with liquid paraffin (B P). When obtaining the specimen the patient's arm was lifted on to the operator's knee, a rubber band was held lightly round the limb at the upper end of the vein in order to prevent reflux of blood, the vein below the selected site was collapsed by the forefinger of the operator's left hand, the needle inserted and 1/3 c c of blood withdrawn. The whole manoeuvre occupied about 15 seconds. This arrest of the venous circulation greatly facilitated rapid venepuncture, and it was considered that, owing to the rapid withdrawal of the small amount of blood required no alteration in composition occurred by reason

of stasis. The exact time was noted the moment the blood entered the syringe. Immediately after withdrawing the needle the contents of the syringe were ejected into a watch glass and the blood drawn up simultaneously into two 1 c.c. pipettes. Without this precaution agreement between the duplicate specimens was found to be unattainable by reason of sedimentation of corpuscles.

Frequent arterial puncture being impracticable, experiments were carried out first in the effort to obtain specimens of capillary blood the composition of which would approximate closely to that of arterial. Foster(9) had shown that the sugar content of the arterial blood of the dog was almost identical in composition with that of capillary blood obtained from the warmed pad. Goldschmidt and Light (11) showed in man that, after immersing the hands in water at 45°C , the veins on the back of the hand yielded blood

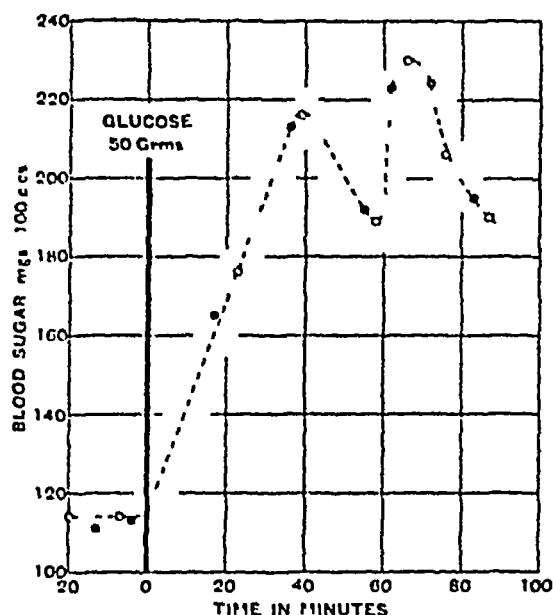


Fig 1 Capillary blood sugar curve after 50 g. of glucose. The discs indicate the blood sugar values of blood taken from the ear, the circles the sugar content of blood taken from the pad of the finger after immersion in water at 45°C .

the oxygen content of which was identical with that of arterial blood. It is, therefore, probable that in the rapid circulation through the warmed hand the blood loses as little sugar as it does oxygen, and a sample of capillary blood from the finger under such conditions would be equivalent to that taken direct from an artery. As it was inconvenient to use the finger and as we had no evidence that warming the part for any length of time did not exert a local influence upon sugar metabolism, an attempt to find a more satisfactory site of withdrawal was made by comparing blood from the warmed finger and freely flowing blood from the lobe of the ear. A young man with glycosuria was chosen for the test. One hand was immersed in

water at 45° C for five minutes before blood was drawn. The finger tip was then rapidly dried with filter paper, the arm elevated and blood taken from the puncture. As soon as possible afterwards blood was drawn from the lobe of the warm ear. Specimens obtained in these ways were taken every fifteen minutes for one and a half hours after the subject had taken 50 g of glucose. The results are shown in Fig 1. It will be seen that the four resting blood sugar values agreed within the limits of error of the Hagedorn-Jensen method and that the figures obtained in samples from either source lie within narrow limits of error, on the same smooth curve. It was decided, therefore, that analysis of frequent specimens of freely flowing capillary blood from the ear would permit the drawing of a curve sufficiently representative of the sugar content of arterial blood for our purpose. The following technique was, therefore, adopted.

Subjects were chosen the lobes of whose ears were slightly smaller than the average. We had found that the most consistent blood specimens were obtained from this type. The lobe was cleaned with a filter paper soaked in ether, a glass pricker bored upwards into the ear (Harrison (15)) and punctures made until the blood flowed freely. The flow was allowed to continue for five minutes before any specimens were taken, it having been noted that specimens taken in that period showed minor discrepancies. The ear was then rapidly dried with an ether-soaked filter paper, a glass pricker dipped in oxalate, reinserted into the puncture, the first drop of outflowing blood wiped away and then the specimen drawn up into the pipette. The procedure was repeated for every specimen, and one puncture usually sufficed for the whole experiment.

In the A-V curves capillary blood samples were taken every 6 to 10 minutes at the commencement of the curve and every fifteen minutes later. In the insulin depression curves every 1½ to 2 minutes at the beginning and every 3 or 4 minutes towards the end. Before the A-V curves were begun usually three specimens were taken for estimating the resting blood sugar level, before the insulin depression curves were begun four samples were always obtained. It will be seen from the figures reproduced that by this technique curves could be obtained in which all the points lay on a smooth curve. For this reason it was considered allowable to connect the charted points with smooth curves, and French drawing curves were used for this purpose. In our opinion the mutual correction of technical errors by frequency of sampling and the accuracy of blood sugar analysis, as shown by the agreement of duplicate estimations in venous blood, make possible the construction of curves of a sufficient degree of accuracy to allow significance to be attached to small variations in contour.

It will readily be appreciated that in experiments performed, even on consecutive days, the resting blood sugar value was not necessarily at the same level. For purposes of comparing different insulin depression curves the following procedure was adopted. The average of the four specimens of blood taken before the injection of insulin was taken as the resting blood

sugar value This value in the first experiment performed on any particular subject was regarded as the standard resting blood sugar level for that person The difference between this figure and the average resting blood sugar concentration in any subsequent experiment was added to or subtracted from all values in that particular investigation so that all the insulin depression curves charted for that particular subject commenced from the same point on the blood-sugar scale In the note at the bottom of each figure is given the standard value and the value of the average resting blood sugar for the experiment under comparison Only curves obtained from the same subject are compared

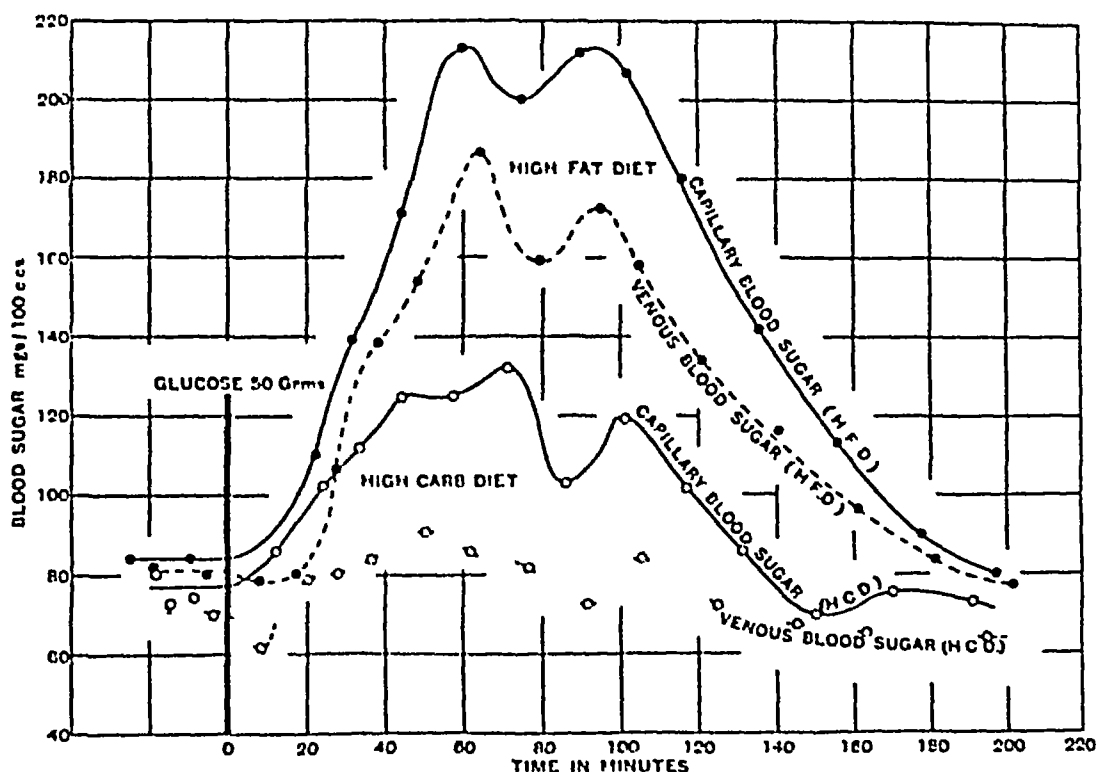


Fig 2 Subject I A V curves obtained after 50 g. glucose by mouth after (1) four days on a high fat diet (H.F.D.) (C 55, P 90, I 160) and (2) six days on a high carbohydrate diet (H.C.D.) (C 658, P 90, I 12) Glycosuria occurred during the test on the high fat diet

For the ordinary depression curves the dose of insulin used was $2\frac{1}{2}$ units of crystalline insulin solution* intravenously This amount was chosen for several reasons Firstly, it did not, as a rule, produce hypoglycæmic symptoms Secondly, it did not depress the blood sugar to such depths that a violent compensatory hyperglycæmia distorted the curve Thirdly, since it produced a distinct, but not maximum, depression it was more likely to reveal small variations in insulin activity than a large dose

The blood sugar was estimated by the Hagedorn-Jensen method but instead of using cotton wool for filtering off the precipitate washed filter paper

* I am indebted to Dr J W Trovan of the Wellcome Physiological Research Laboratories for the solution of crystalline insulin

was used as recommended by Kramer and Steiner (19) No 589, White Label, Schleicher and Schull papers were very satisfactory. The error of the Hagedorn-Jensen method is usually given as ± 2 mg per cent but our results on the duplicate estimations of venous blood suggest that the error is nearer ± 1 mg per cent. Accurately calibrated blood pipettes were necessary as errors in them of 2% became manifest as corresponding discrepancies in blood sugar values. Venous blood samples were always analysed in duplicate but this was not possible in the capillary or "arterial" blood samples.

RESULTS

The A-V glucose tolerance curves

The venous deviation and the venous step

On consideration of Fig 2 it will be seen that variations in the venous curve reflect corresponding variations in the capillary blood curve save in the initial phase of hyperglycaemia (Figs 3, 5, 6 and 7) where the following sequence of events occurs. Immediately after the commencement of the hyperglycaemia the A-V difference increases, it then rapidly decreases and then once more increases again (Fig 3). The effect of these three variations is to produce in the venous blood sugar curve a deviation from parallelism with the capillary blood sugar curve such that the venous curve becomes S shaped. This irregularity we have referred to as the "venous deviation". As this phenomenon is called into existence by the three consecutive variations in the A-V difference we have referred to these in relation to it as the first, second or third stages of the venous deviation. On the advent of the third stage the venous sugar curve changes its direction abruptly so as to make a sharp angle with the line it traced during the second stage. The result is the production in the curve of a step the edge of which is directed towards the arterial blood sugar curve. Depending as it does on the onset of the third stage this phenomenon is the essential part of the venous deviation and we have termed it the "venous step".

In Fig 3 the initial phases of the curves shown in Fig 2 are drawn on a larger scale. The high carbohydrate curve in this case shows an unusually rapid immediate increase in the A-V difference, and as this depends upon the first venous blood sugar value after glucose (duplicate analyses 62, 62 mg/110 c.c.) a curve from another subject with a more usual type of first stage is given in Fig 5. A good example of the venous deviation on a high fat diet is shown in Fig 6, whilst in Fig 7 the venous deviations on the two types of diet are shown in a subject having the high carbohydrate curve characterised by a high initial peak. The above curves are representative of the results obtained under the differing conditions of our experiments.

The presence of the venous step being a point of primary importance in the discussion of these results, the possibility that it owes its existence to an artefact must be considered.

curve at that particular time. At the beginning, insulin action is dominant, at the end, the glycogenolytic mechanism, and in the intervening time the two processes strive for ascendancy. We have found that, as a rule,

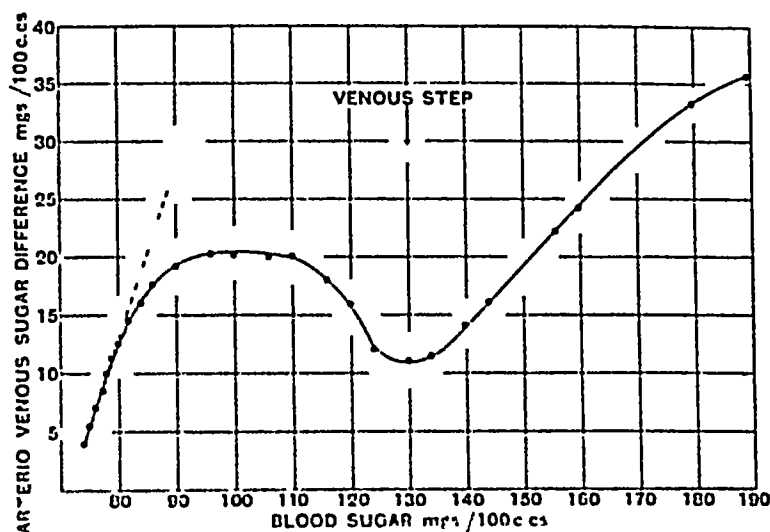


Fig 1 Curve obtained by plotting the capillary blood sugar mg/100 cc against the corresponding A-V difference in the experiment on the high fat diet shown in Fig 3

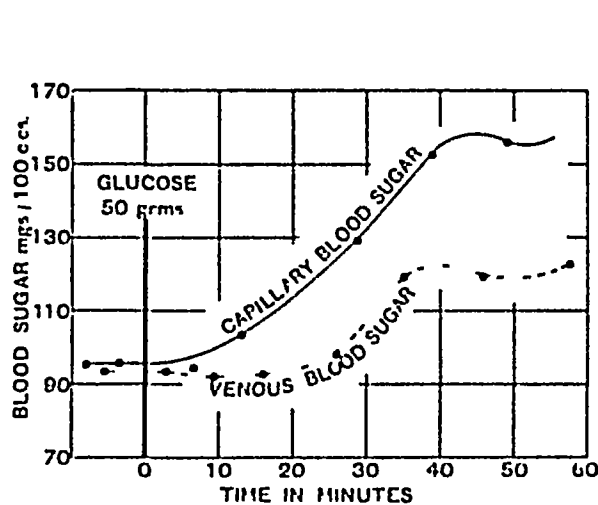


Fig 5

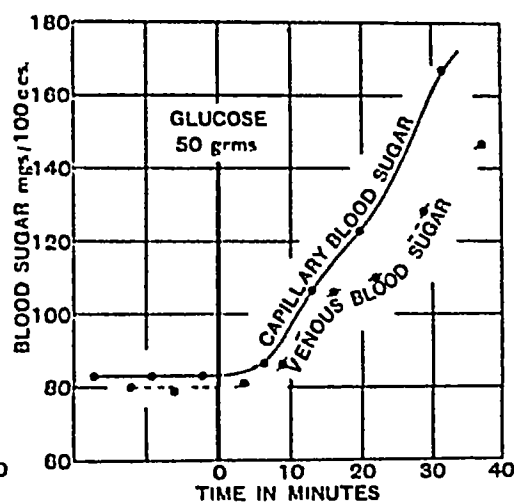


Fig 6

Fig 5 Subject V A V curve after 50 g glucose when subject had been for six days on high carbohydrate diet (C 610, P 90, F 42)

Fig 6 Subject IV A V curve after 50 g glucose when subject had been taking for eight days a high fat diet (C 55, P 88, F 190)

glycogenolysis establishes its preponderance earlier when the subject has been on a starchy diet or received preliminary doses of glucose. Thus in Fig 11, when the subject was on a high fat diet the first sign that the fall of

blood sugar was being opposed is shown, in all three experiments, by a kick in the curve at 15 minutes, but when the subject had received preliminary doses of glucose, a kick appeared at 5 minutes (Figs 16 and 17). There is thus a tendency for compensatory liberation of sugar into the blood to mask the activity of insulin on a high carbohydrate diet. For this reason, when it was desired to investigate the action on the blood sugar of different doses of insulin and to obtain as complete a picture as possible of pure insulin effects it was necessary first to allow the subject to become stabilised upon a high fat diet (Figs 11 and 12). The shape and fall of the curve is so constant under the same conditions that practically superimposable curves

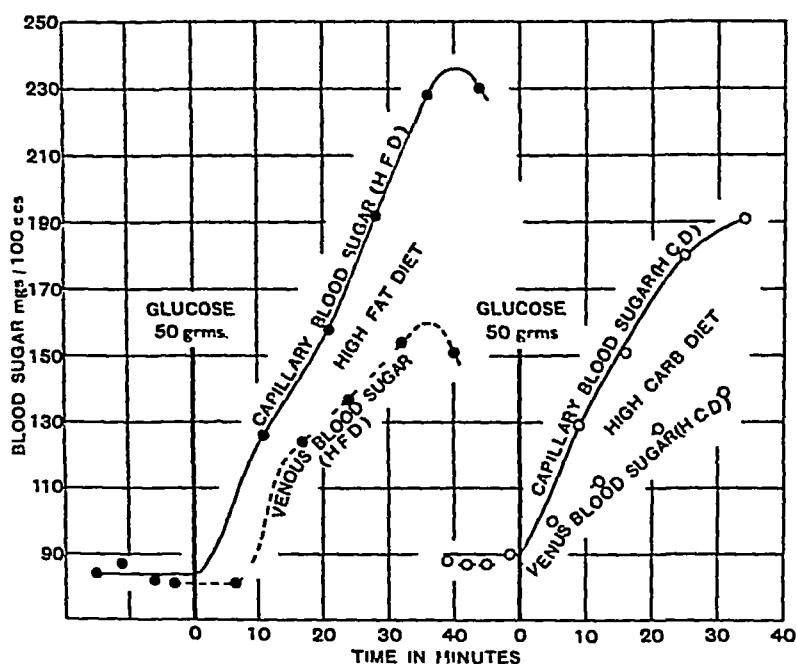


Fig 7 Subject II A V curves after 50 g glucose after (1) eleven days on high fat diet (H F D) (C 55, P 88, F 202), and (2) twelve days on a high carbohydrate diet (H C D) (C 659, P 88, F 42). The high carbohydrate curve is of the type characterised by the high initial peak.

are obtained. Reference to Fig 11 will indicate the degree of precision attainable when blood samples are taken by the above technique at such short intervals. The 5 and 10 unit depression curves have been found to coincide and the slight difference in this case may be explained by the different degrees of initial hyperglycæmia provoked by the different doses. Thus hyperglycæmia does not occur after injection of crystalline insulin but invariably occurs after the intravenous injection of other preparations (Figs 11 and 12).

Figs 11, 12, 13, 15, 16 and 17 show that immediately after the injection of insulin there is a short latent period in which no demonstrable fall of the

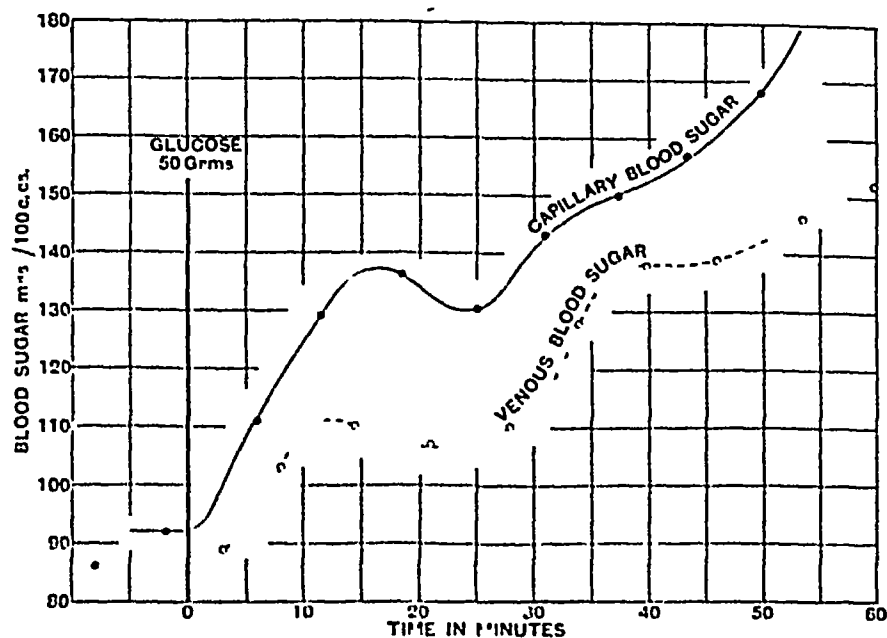


Fig 8 Subject III A V curve after 50 g of glucose Subject had been for nine days on a high fat diet (C 55, P 88, F 202) This type of curve with two steps was obtained in all six glucose tolerance curves performed on this subject

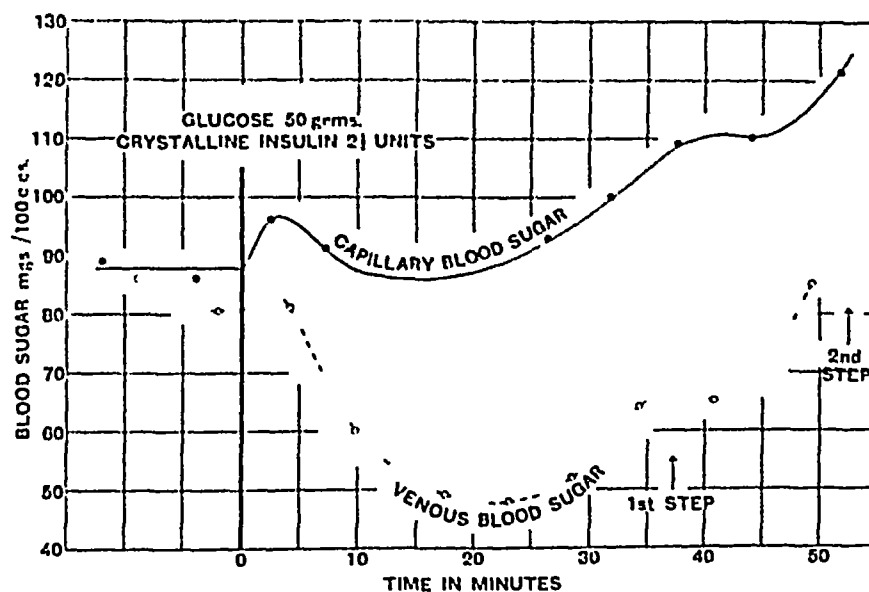


Fig 9 Subject IV Effect of administration of 50 g glucose and 45 seconds later 2½ units of CRYSTALLINE insulin solution Subject had been for sixteen days on a high fat diet (C 55, P 88, F 100)

blood sugar is detected In Fig 13 is recorded the effect on the blood sugar of two injections of 2½ units of crystalline insulin solution given intravenously

at an interval of 13½ minutes. A latent period will be seen to occur after each injection. The experiment demonstrates that this latency of insulin action occurs even when the organism is already under the influence of that substance. In every case the latent period is followed by a phase in which the blood sugar falls with increasing velocity to reach its maximum point of depression. The significance of these observations will be discussed later.

In Figs 11 and 12 the effects on the blood sugar level of different doses of insulin are demonstrated. It is shown that the time at which the lowest level of glycaemia is reached is practically independent of the dose of insulin, and also that above a certain maximum dose (5 units in Fig 11) increasing the amount of insulin injected neither shortens the latent period nor

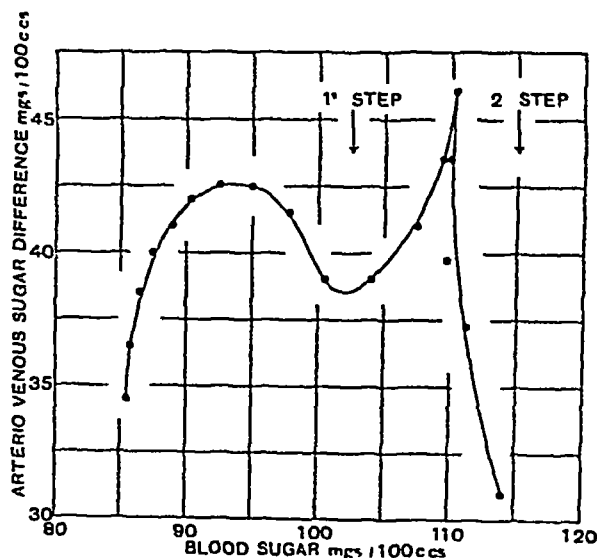


Fig 10 Curve obtained by plotting the capillary blood sugar mg/100 c c against the corresponding A V difference in the experiment recorded in Fig 9

accelerates the rate of depression (Fig 11). Below this maximum dosage increase in the amount of injected insulin shortens the latent period slightly and increases the velocity of depression considerably (Figs 11 and 12). These two figures also show that the degree of fall of the blood sugar is not directly proportional to the insulin dosage.

Fig 14 records the changes in the A-V difference following the injection of 15 units of ordinary insulin (non-crystalline). It will be seen that throughout the latent period the A-V difference remains practically the same as it was before insulin was injected and that in the phase of increasing depression the A-V difference increases with accelerated velocity.

Fig 15 shows insulin depression curves obtained, the one on a high fat, the other on a high carbohydrate diet. The greater drop and the accelerated rate of fall under the latter regime are well shown.

As can be seen in Fig 2 the diet containing much carbohydrate is also associated with a small degree of hyperglycaemia Hamman and Hirschman (14) showed that if two consecutive tolerance curves were performed the second was lower and shorter than the first Staub (29) and Foster (9) have also investigated this phenomenon It was accordingly determined to observe the insulin depression curve after previous administration of glucose

The phenomenon reported by the above authors was first confirmed on the subject Previous to this investigation all experiments had been performed at 10 a m and it was necessary first to perform a control experiment showing that the depression curve at 2 p m was not materially different from that at 10 a m Our result showed a very slightly accelerated depression

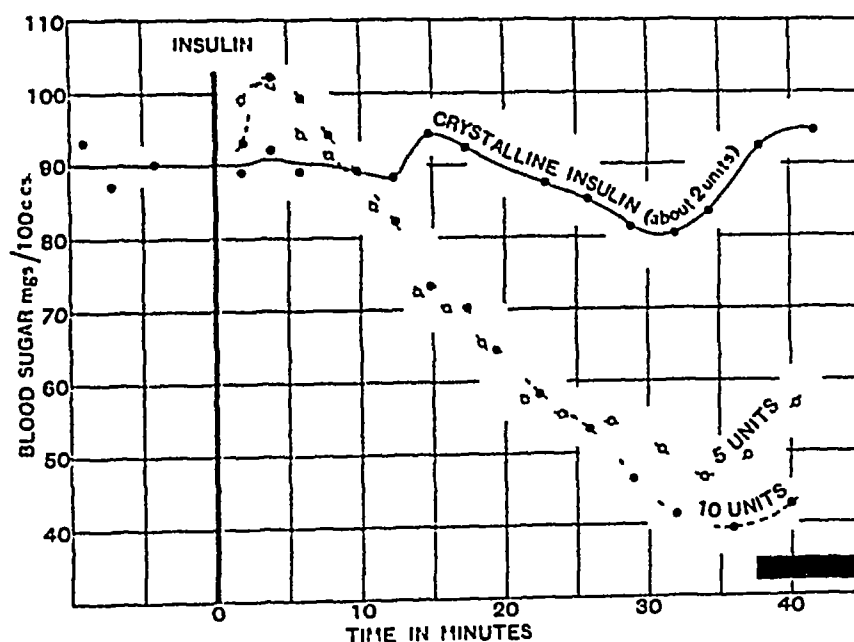


Fig 11 Subject III Insulin depression curves after 10 and 5 units of ordinary insulin and approximately 2 units of crystalline insulin all performed whilst the subject was taking a high fat diet (C 55, P 88, F 202) The 10 unit curve was performed after the subject had been on this diet for 15 days, the 5 unit curve was taken two days later and the 2 unit curve one day after this Standard resting blood sugar, 10 unit curve, 90 mg/100 c c Average resting blood sugar, 5 unit curve, 89 mg/100 c c, 2 unit curve, 78 mg/100 c c The shaded rectangle represents the time during which hypoglycæmic symptoms were observed after the 5 and 10 unit doses The time of onset was about 37 minutes after each dose After 5 units the symptoms ceased spontaneously about 44 minutes but after 10 units they were so severe that they were cut short at 41 minutes by giving glucose

at 2 p m After 140 g of glucose, given in three doses during the night, 50 g of glucose was given to the patient at 10 a m and insulin $2\frac{1}{2}$ units at 2 p m The glucose tolerance curve at 10 a m was lower than the ordinary curve for this patient at that time The marked effect manifested by insulin at 2 p m is shown in Fig 16 It is worthy of note that this is the only

occasion on which symptoms of hypoglycaemia have developed after $2\frac{1}{2}$ units of insulin. A further experiment was performed in which 50 g of glucose were given at 8.35 p.m., 12 a.m., 2 a.m., 4 a.m., 6 a.m. and insulin ($2\frac{1}{2}$ units) injected at 10 a.m. The result is shown in Fig. 17. Potentiation is there but is less pronounced than in the first curve. It should be noted that the subject's sleep was not materially affected by these frequent nocturnal draughts and that these two experiments were performed on the same subject but have been repeated on other individuals.

The effect of diet upon the glucose tolerance curve and upon the insulin depression curve

In Fig. 2 are shown the A-V curves of the same subject on a high fat and on a high carbohydrate diet. The difference in the degree of hyperglycaemia under standard conditions after 50 g of glucose is well shown. In this particular case the caloric value of the high fat diet was lower than that of the high carbohydrate diet but the same variation in tolerance was obtained in experiments when the caloric values were approximately the same. The majority of the high carbohydrate curves were of the "low" type shown in Fig. 2 but another variation has been encountered (Fig. 7). In this type the curve rises rapidly to the neighbourhood of 180 mg/100 c.c. then falls rapidly to hypoglycaemic levels and continues at low figures. The subject who gave this latter curve showed the usual high and prolonged hyperglycaemia on a high fat diet.

Figs. 3 and 7 show that on the high carbohydrate diet the venous step occurs earlier than on the high fat diet. Fig. 15 shows that the same dose of insulin exerts a more rapid and greater effect upon the resting blood sugar when the subject is on a starchy than when on a fatty diet. Thus a more rapid development of the venous step occurs under the same conditions as those which occasion a greater degree of activity of the injected insulin.

On a high carbohydrate diet our subjects showed a greater capacity to deal with sugar than on a high fat diet, for on the latter diet the various investigations gave results which tended to approximate quantitatively to the findings in diabetes, whilst on the former diet the tendency was in the opposite direction. On the high fat diet the approximation to the metabolic findings in diabetes was demonstrated by the presence of ketone bodies in the urine, and by a diminished tolerance for carbohydrate revealed by the occurrence of glycosuria and abnormally high blood sugar curves with a small A-V difference, after oral administration of glucose. The contrast was shown on the starchy diet by the continued absence of ketonuria, and after the ingestion of glucose by the absence of glycosuria, the lower degree of hyperglycaemia and the development, at lower blood sugar levels, of a greater A-V difference. Thus it will be seen that under the conditions of our experiments, the production of an increase in the ability of the subject to deal with ingested glucose was always associated with an apparent increase in the activity of the insulin injected.

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DISCUSSION

The significance of the insulin depression curve

Immediately after the injection of insulin there is a period during which no depression of the blood sugar can be detected. The question arises as to the cause of the latent period. Is it due to insulin requiring this time to reach its site of action in the tissues, or is it due to the injected insulin being inactive when it reaches the tissues and requiring this time to develop its activity? If the first or these two conceptions is correct then there appear to be three possible explanations. The first is that insulin may not have been distributed through the circulation. The second, that before insulin can act it must diffuse into the cells and the latent period represents the time taken for this penetration, the third, that insulin may

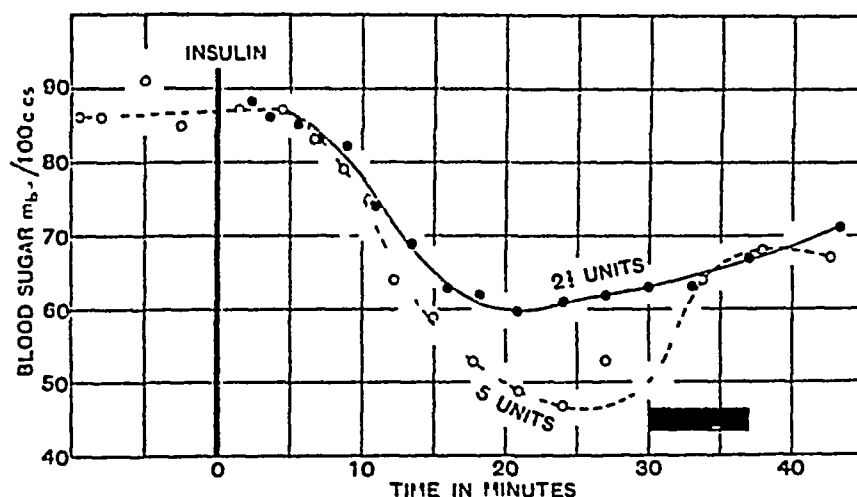


Fig. 12 Subject IV Insulin depression curves after 5 and $2\frac{1}{2}$ units of crystalline insulin solution. 5 unit curve after eleven days on high fat diet (C 55, P 88, F 190), $2\frac{1}{2}$ unit curve two days later. Standard resting blood sugar, 5 unit curve, 86 mg/100 c c. Average resting blood sugar, $2\frac{1}{2}$ unit curve, 89 mg/100 c c. The shaded rectangle represents the duration of hypoglycemic symptoms after 5 units of insulin.

have been held up in some central organ, such as the liver, changed there into an active form and time taken in this way.

The following considerations negate the first possibility. When insulin preparations other than a solution of the crystalline produce are injected an initial hyperglycemia occurs (Fig. 11). This phenomenon is more marked, after the injection of the same preparation of insulin, when the subject's glycogen stores have been filled by a diet rich in carbohydrates than when they are at a low level after a diet consisting mainly of fat. The hyperglycemia, therefore, probably indicates liberation of glucose from glycogen. As insulin was always given intravenously the glycogenolytic impurity must have been transported by venous blood to the heart, by arterial blood to the glycogen store, glucose liberated from here into the venous blood, carried

back to the heart and redistributed in the general circulation before the hyperglycemia could be detected in the capillary blood. This rise of blood sugar can be demonstrated within two minutes and so there is no doubt that insulin itself could have been distributed throughout the vascular system in that time (Fig 11). Yet the latent period may last as long as 8 or 10 minutes (Fig 13).

If the second possibility, that this period represents the time of diffusion of insulin into the cells, is correct then one would expect that, if the concentration of insulin in the blood were increased by injecting larger amounts of insulin into the circulation, diffusion would be accelerated and the latent period correspondingly reduced. Fig 11 shows that when 5 or 10 units were injected the latent period remained the same.

The third possibility, that insulin may be changed in the liver is disproved by the work of Mann and Magath (22) and Burn and Dale (5) showing that insulin acts peripherally in the absence of the liver, and by the experiments of Frank, Nothmann and Wagner (10a, 10b) showing that after intra-arterial injection of insulin the A-V difference is most marked in the limb supplied by that artery.

The first conception, therefore, fails to be satisfied by any of the three possible explanations.

Fig 9 shows the effect of simultaneous administration of 50 g of glucose and $2\frac{1}{2}$ units of *crystalline* insulin. It will be seen that the insulin did not exert its action sufficiently rapidly to restrain an initial alimentary hyperglycemia. At the commencement of the paper, reasons were put forward on which the assumption that the A-V difference is a measure of the active insulin in the tissues, was based. Fig 14 demonstrates that during the latent period there is no increase in the A-V difference, i.e., that during this period there is no increase in the concentration of active insulin in the tissues.

It appears then that the second conception is tenable—that after insulin injection this period of unaffected blood sugar level represents the time which injected insulin requires to develop detectable activity *after it has reached the tissues*.

The demonstrable fall of blood sugar commences at the end of the latent period and proceeds with increasing rapidity. The action of insulin upon the blood sugar, therefore, is one which proceeds with acceleration of velocity and can be represented by the curve shown in Fig 18. It is necessary at this point to consider the results obtained when different doses of insulin are injected intravenously. The two sets of results, shown in Figs 11 and 12, were obtained each on different subjects, both of whom were on a high fat diet. All the experiments in both cases were performed within a few days of each other and under exactly the same conditions. In Fig 12 the effects of $2\frac{1}{2}$ units and 5 units of crystalline insulin solution upon the resting blood sugar of subject IV are shown, in Fig 11 the effects of 5 and 10 units of ordinary insulin (Wellcome Brand, Hospital packing), and of a solution of crystalline insulin containing between 1 and 2 units, upon subject III are

demonstrated Fig 14 shows the effect under identical conditions of 15 units of ordinary insulin (drawn from the same phial as used for subject III) upon subject II, and the latent period, rate of fall, and depth of depression are identical with those obtained on the 10 unit curve in Fig 11 In Fig 11 it is shown that the maximum depression with 5 units is 45 mg/100 c c, with 10 units 52 mg/100 c c and, in Fig 11, a dose of 15 units produces a fall of approximately 50 mg/100 c c Fig 12 gives the fall with 2½ units as 27 mg/100 c c and with 5 units as 10 mg/100 c c It appears, therefore, that if a certain amount of insulin produces a fall from a definite resting blood sugar level of a particular degree, then more than double that amount of insulin will be required, under the same conditions, to produce double that

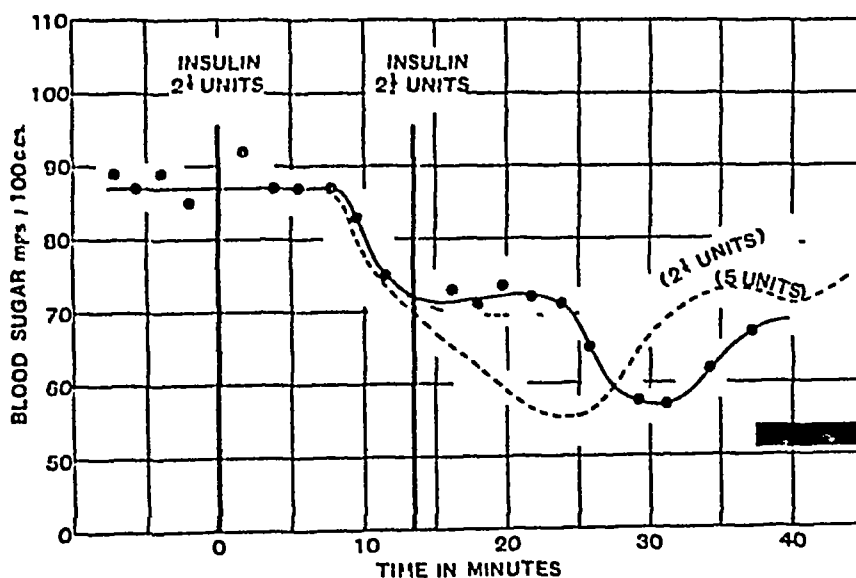


Fig 13 Subject VI Insulin depression curve showing the effect of two consecutive doses of 2½ units of crystalline solution, the second dose being given 13½ minutes after the first For twelve days previously the subject had been taking a high fat diet (C 56, P 87, F 255) The broken curves show the effect of a single dose of 2½ units and of 5 units of crystalline insulin solution on the same subject These latter curves were obtained under the same conditions as in the former experiment but during a previous stay in hospital The shaded area represents the time during which hypoglycemic symptoms were observed after the second dose of 2½ units of insulin

degree of depression The lowest blood sugar we have recorded was 32 mg/100 c c in venous blood and according to Somogyi (28) the non-fermentable reducing substances of blood have a value of about this figure The depression curve after 10 units (Fig 11) fell to 39 mg/100 c c and at this stage little fermentable sugar can have remained in the blood It is not surprising, therefore, that there is a maximum dose of insulin, apparently about 10 units, beyond which no increase can produce a greater degree of depression

It is of more significance that whilst increasing the dose of insulin up to a certain maximum accelerates the rate of fall, further increase neither shortens the latent period nor accelerates the lowering of the blood sugar (Figs 11 and 12). In Fig 11 it will be seen that increasing the dose from 5 to 10 units produced no acceleration of depression nor diminution of the latent period, and Fig 14 shows that no greater effect was secured by using 15 units. There thus appears to be some factor other than the amount of insulin available which limits the rate of depression, and the nature of this limiting factor must now be considered.

Despite the observation that increasing the dose of insulin beyond a certain maximum neither shortens the latent period nor accelerates the rate of depression, in the experiments shown in Figs 15 and 17 the latent period has been shortened and the rate of fall has been accelerated by feeding large quantities of carbohydrate. Thus the unknown factor limiting insulin action is susceptible of alteration.

This observation is the more striking because of its paradoxical nature. By previous and prolonged administration of carbohydrate the glycogen stores must have been augmented (Hynd and Rotter (18)), yet despite the fact that the very depots to which blood sugar is removed are relatively full of carbohydrate, the blood sugar is removed more rapidly under the action of insulin than when these depots are relatively empty after a diet containing little carbohydrate and much fat.

In considering these results it must be remembered that our data are confined to observations on the rate of removal of the blood sugar. Variations in this rate may be caused by alterations in one or two broad ways. Firstly, the mechanism by which sugar is abstracted from the blood may be rendered more efficient so that in response to the same amount of insulin, sugar is removed more rapidly under one set of conditions than another. Secondly, insulin itself may become more efficient, so that under one set of conditions at any particular time after injection, the blood sugar concentration may indicate the same effect as if a larger dose had been injected under another set of conditions. The limiting factor, therefore, may act either on the mechanism for removal of sugar, or on insulin itself. The former possibility will be considered first.

There are two obvious hypothetical ways by which the action of the mechanism for removal of the blood sugar may be limited. There may be a limit to the rate at which sugar can be removed from the blood, there may be a lag in bringing the abstracting mechanism into action.

The first hypothesis explains easily the observation that increasing the dose of insulin above a certain maximum does not accelerate the rate of fall of the blood sugar, but it gives no explanation of the fact that increasing the agent which results in the removal of sugar, namely insulin, does not proportionately shorten the latent period when the blood sugar is not being withdrawn at all (cf Figs 11 and 12).

On the lag hypothesis delay may occur in at least two places. There may be delay in the transference of sugar from the blood to the cells, or there may be delay at the stage in which the free intracellular glucose is changed into another form, thus causing a dependent delay in diffusion of sugar from the blood into the cell. The former alternative will be considered first.

We know that insulin acts peripherally. In Fig 14 it can be seen that after injection the A-V difference markedly increases. At 15 mins the "arterial" blood sugar has fallen 22 mg/100 c.c. and the A-V difference has increased by 25 mg/100 c.c. It, therefore, appears probable that the major portion of the sugar removed from the blood under the agency of insulin, is transferred to the systemic tissues. As far as we know insulin does not

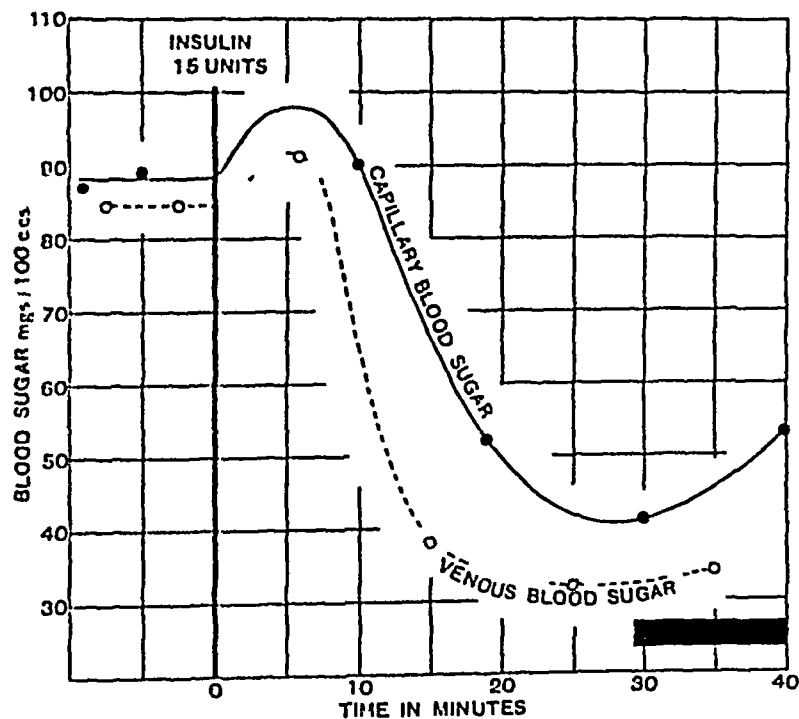


Fig 14 Subject II A-V insulin depression curve with 15 units of ordinary insulin after subject had been for seven days on a high fat diet (C 55, P 88, F 202). The shaded area shows the time during which hypoglycemic symptoms were observed. Glucose was given at 33 minutes.

act in the blood stream but in the cells, so that changes in concentration of sugar in the tissues must necessarily precede changes in concentration of sugar in the blood. Now hypoglycemic symptoms occur when the blood sugar is low and are almost certainly related not to the level of blood sugar but to the level of sugar in the tissues. If, therefore, there is a lag in the removal of sugar from the blood to the tissues hypoglycemic symptoms should precede the time of maximum depression of the blood sugar. In

twelve experiments in which hypoglycæmic symptoms were produced they invariably occurred *after* the maximum depression time. Figs 11, 12, 13 and 14 will suffice to illustrate this point but further results bearing on the peculiar discrepancy will be brought forward later. It is improbable, therefore, that there is a lag in the actual transference of sugar from the blood to the cells.

The second alternative of an intracellular lag is disproved by the experiment shown in Fig 13. In this experiment two doses of 2½ units of crystalline insulin solution were given intravenously, the second dose 13½ minutes after the first. It will be seen that the second dose was injected into the circulation at the time when the first dose was exerting a marked effect on the blood sugar. Now if there is an intracellular lag the first dose has, at the time of the second injection, overcome this obstacle to the storage of the blood sugar, and, therefore, the second dose should depress the blood sugar immediately it is injected, i.e., there should be no latent period. It is found, however, that after each dose there is a definite latent period approximately 8 minutes after the first dose and 10 minutes after the second. The lag hypothesis appears, therefore, to be untenable and the observation that in this experiment a latent period occurs after each injection of insulin points to the conclusion that this latent period is definitely referable to some characteristic of insulin action.

From these considerations it would appear improbable that the unknown factor acts on the mechanism by which sugar is abstracted from the blood, and consequently, variations in the rate at which the blood sugar is removed after injection of insulin are not attributable to variations in efficiency of this abstracting mechanism. It remains to consider the possibility that the unknown factor acts on insulin itself.

After injecting insulin the change in the blood sugar, in the early part of the depression proceeds as shown in the curve of Fig 18, and as the blood sugar level remains unchanged until insulin is injected, then this curve must also represent the development of the action of insulin. The unknown factor, therefore, limits the rate of development of insulin action in accordance with the reaction curve of Fig 18. From this point of view this factor may be one of two things. It may either be an inhibitor, which is removed after insulin injection with increasing velocity thus permitting insulin to manifest an increasing effect, or it may be an activator which reacts with injected insulin to produce an active product, the reaction of activation occurring with accelerating velocity.

If the factor is an inhibitor then its removal must be brought about through the action of the insulin injected. This being so, then the injection of large doses of insulin should produce a more speedy removal, with the result that the action of insulin on the blood sugar would be manifested in a shorter time and at a greater rate. This has been shown not to occur. Similarly, if the latent period is due to the presence of an inhibitor, once the blood sugar commences to fall the major portion of the inhibitor has been

removed and the injection of a second dose of insulin should result in an immediate further fall of the blood sugar, i.e., there should be no latent period after the second injection. Fig 13 shows this is not so. The conception of the unknown acting as an inhibitor of insulin appears, therefore, to be improbable.

If the factor is an activator, then activation must occur in accordance with Fig 18. This reaction curve suggests the analogy of the autocatalytic activation of trypsinogen by enterokinase, and all the results discussed can be explained on the basis that insulin is activated by the unknown factor in a similar manner.

A further consideration of Figs 11 and 12 will reveal the important result that the maximum degree of depression is reached at approximately the same time after injection of insulin whatever the dose administered, and whatever the depth of depression. The lowest point of all the curves in

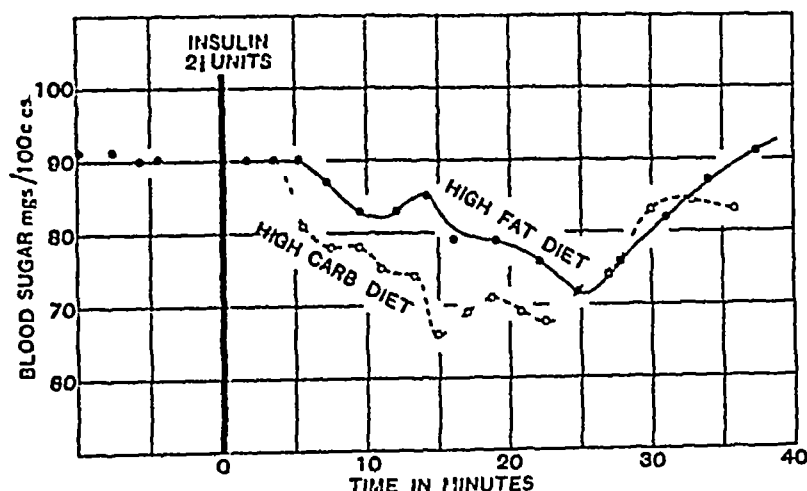


Fig 15 Subject III Insulin depression curve (21 units crystalline insulin solution) —
 (1) after eight days on a high fat diet (C 56, P 87, F 255) Standard resting blood sugar 90 mg/100 cc
 (2) after thirteen days on a high carbohydrate diet (C 659, P 90, F 42)
 Average resting blood sugar 84 mg/100 cc

Fig 11 occurs from 32 to 35 minutes and in Fig 12 from 23 to 26 minutes. Further it will be seen that the latent period in each set of curves is of approximately the same duration. Apparently the time required by insulin to manifest detectable activity, and to attain a maximum effect on the blood sugar is independent of the dosage. We have previously noted that below a certain maximum dose the degree and rate of depression is influenced by the amount of insulin given whilst above this maximum dose such influence is absent. The above and the previously discussed results regarded as manifestations of the action of an activator may be explained in the following way.

The observation that increasing the dose of insulin above a certain maximum does not accelerate the manifestation of insulin activity, is explained on the grounds that the amount of active insulin produced per unit of time is limited by the concentration of activator present in the tissues, any excess of insulin remaining temporarily outside the scope of the reaction. The maximum dose of insulin is the amount required to bring into action all the activator present in the tissues. Doses below the amount leave a relative excess of activator outside the field of reaction and this excess reveals its presence only when larger doses of insulin are injected. Hence below the maximum dose the rate of depression of the blood sugar may be increased by increasing the amount of insulin injected. The latent period is explained by the autocatalytic nature of the reaction, and the constancy of the maximum depression time by the percentage conversion rate of insulin to active substance being determined by the concentration of activator present.

Thus the hypothesis we arrive at, from a consideration of the insulin depression curves, is that insulin is activated by an unknown factor in an autocatalytic manner, and that in this reaction insulin behaves as a substrate and the unknown as a kinase.

Significance of the venous deviation and the venous step

The venous deviation is produced by a sequence of variations in the A-V difference. The phenomenon is made up of three stages, in the first stage the difference increases, in the second decreases, and in the third rapidly increases again (Figs 2, 3, 4, 5, 6, 7 and 8).

On examining the first stage it will be seen that the A-V difference increases roughly in proportion to the rise in capillary blood sugar (Fig 4). In a previous paper (Himsworth (16)) it was suggested that the glucose in the blood and the active insulin in the tissues bear a relationship to each other which conforms with the Mass Action Law. A corollary of this theory is that increasing the glucose in the blood, whilst the active insulin concentration is maintained unchanged in the tissues, will cause an acceleration of this reaction velocity, with a resulting increase in the rate of removal of glucose from the blood, i.e., the A-V difference will become greater. It is suggested that the greater A-V difference in the first stage can be explained, not by a raising of the concentration of active insulin in the tissues but by the acceleration of interaction with the same concentration of active insulin which was present before glucose was given.

In the second stage we see the A-V difference diminish despite the continued rise of blood sugar. In the first step in Figs 9 and 10 the artificial production of a venous deviation by the simultaneous administration of insulin and glucose is shown. By comparison with an insulin depression curve on the same patient, it can be seen that at the same time that the action of insulin wanes in Fig 12, diminution of the A-V difference is occurring in Fig 9. This supports the deduction, presented at the commencement of

this paper, that the A-V difference is an index of the concentration of active insulin in the tissues, and it appears allowable to conclude that the second stage of the venous deviation is produced by a rapid depletion of the active insulin originally present in the tissues. Hyperglycaemia appears to occasion the more rapid utilisation of tissue insulin.

The first two stages can, therefore, be explained as manifestations of the active insulin concentration present in the tissues when the glucose was given, and so far there is no evidence that the concentration of active insulin is being increased, at the periphery, at a faster rate than was occurring before hyperglycaemia was produced.

The third stage is characterised by a sudden increase in the A-V difference, an increase so rapid that in some cases (Fig 8), despite the continued absorption of glucose, the sugar content of the arterial blood is drawn

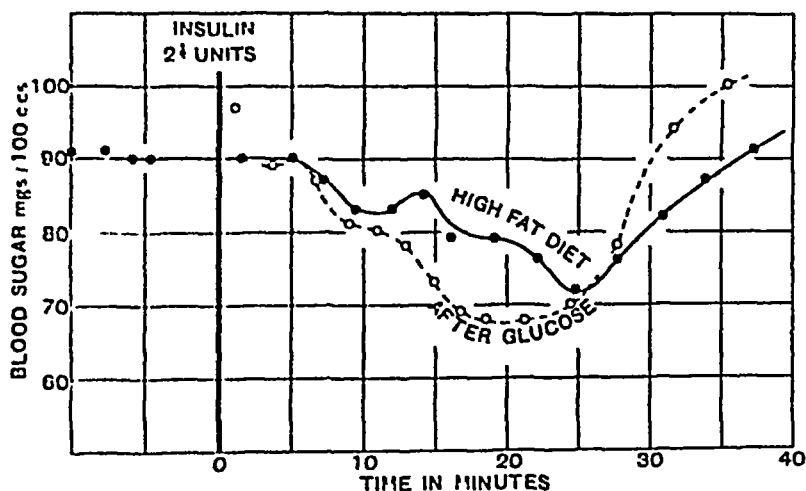


Fig 16 Subject III Insulin depression curves ($2\frac{1}{2}$ units crystalline insulin solution) —
 (1) after eight days on a high fat diet (C 56, P 87, F 255)
 Standard resting blood sugar 90 mg/100 c c
 (2) on same diet after 40 g glucose at 10 p m, 50 g glucose at 2 a m, 6 a m and 10 a m
 Insulin at 2 p m
 Average resting blood sugar 80 mg/100 c c

down to lower levels. There appears to be no other explanation than that at this stage there occurs a rapid augmentation of the concentration of active insulin present in the tissues. The question now arises as to why this increase is delayed until the time of onset of the third stage.

The most obvious explanation is that insulin is not secreted until this point. Zunz and la Barre (33) and Grafe and Meythaler (12) have shown that a rise of blood sugar stimulates the pancreas to secrete insulin. But it is extremely difficult to accept any view which implies an explosive secretion of this substance in response to hyperglycaemia. On reference to Figs 2 and 3 it will be seen that, whilst the venous step occurs in both curves, the capillary blood sugar, throughout the high carbohydrate curve, never attained

that level which on the high fat diet corresponded to the third stage of the venous deviation. The third stage does not, therefore, appear to depend upon any fixed critical level of arterial hyperglycemia. An explanation that has been suggested of the low curve after glucose, on the high carbohydrate diet, is that the ingestion of large quantities of carbohydrate has sensitised the insulin secreting mechanism to the stimulus of hyperglycemia. An objection may, therefore, be raised to the conclusion drawn from Figs 2 and 3 on the grounds that the critical level of blood sugar initiating insulin secretion has fallen under the stimulus of carbohydrate feeding. But we also possess another two curves from the same subject, under slightly modified conditions, the one upon the high fat diet and the other upon the high carbohydrate diet. In the high fat curve of Fig 2 the capillary blood sugar rose 60 mg from the resting level before the third stage of the step appeared, in the second, (unrecorded) high fat curve this stage was reached when the blood sugar had risen only 25 mg. In the high carbohydrate curves the level rose 15 mg in both cases. In two other high fat curves on Subject II this same result was obtained. None of these experiments indicate that the degree of hyperglycemia bears any relation to the development of the third stage.

A further point against a sudden secretion of insulin is that at no other point in the A-V curve is there a divergence suggesting a marked variation in the active insulin concentration in the tissues. After the step the venous curve follows and reflects the capillary blood curve (Fig 2) so that finally a gradual convergence occurs which again brings the A-V difference to approximately normal values.

On general grounds it appears improbable that insulin is secreted only when a definite degree of hyperglycemia has been reached. The gradual rise of blood sugar following pancreatectomy demonstrates the importance of the pancreas in maintaining the blood sugar at a constant level, yet if insulin secretion only occurs at a critical level of hyperglycemia, periodic variations in glycemia in the intact animal would be inevitable. Further, the blood sugar is known to remain remarkably constant during exercise. Carbohydrate is burnt under these conditions, and as the liver glycogen becomes depleted, glucose must have been removed from the blood. We have brought forward evidence (*vide supra*) that, when increased abstraction of blood sugar is occurring, the tissue insulin concentration tends to fall at a more rapid rate. Artificial restriction of tissue insulin, as by pancreatectomy, occasions hyperglycemia and as the blood sugar does not change during exercise, it would appear that despite the depletion of tissue insulin, the appropriate concentration of insulin is maintained in the tissues in the absence of the stimulus of hyperglycemia.

Thus from our results and on general grounds, it appears unlikely that insulin is secreted intermittently and much more probable that it is given out continually but, during increasing hyperglycemia, at a gradually increasing rate. In this case insulin must have been secreted during the first

and second stages of the venous step and yet have only manifested its action at the third stage. The increase in the A-V difference here is much too abrupt to be explained on the grounds of progressively increasing secretion, and this sudden burst of activity would appear to signify that, at the time of the third stage, the insulin previously secreted rapidly developed its activity.

From the arguments just discussed the onset of the increasing rate of secretion may be taken as the time at which hyperglycemia first appears, and for practical purposes this can be regarded as coincident with the ingestion of glucose. If newly secreted insulin requires time to develop its activity then there should be some relationship between the time of onset of the increasing secretion and the development of the third stage. This relationship we have shown to exist. The step occurs at a definite but

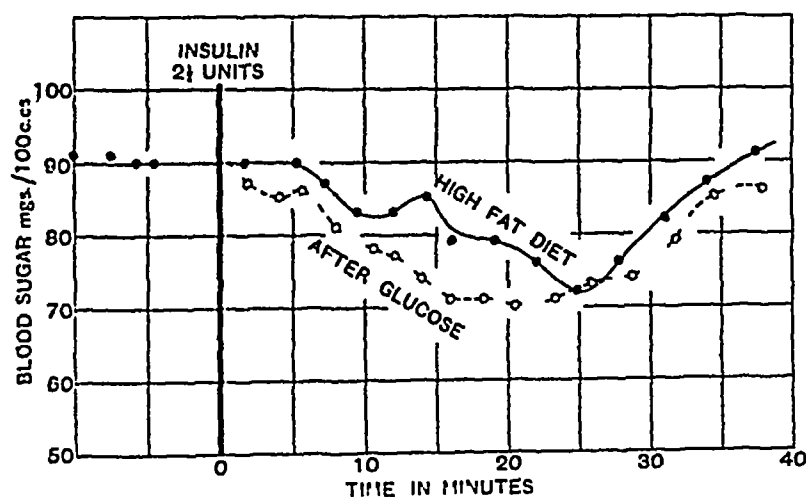


Fig 17 Subject III Insulin depression curves ($2\frac{1}{2}$ units of crystalline insulin) —

(1) after eight days on a high fat diet (C 56, P 87, F 255)

Standard resting blood sugar 90 mg/100 c c

(2) On same diet after 50 g glucose at 8 35 p m, 12 a m, 2 a m, 4 a m, 6 a m Insulin at 10 a m

Average resting blood sugar 96 mg/100 c c

slightly varying time after glucose has been taken, and this time is practically constant on any particular diet.

The observations thus suggest that the time before the venous step appears is the time required for insulin to develop detectable activity. As it is considered that insulin has been secreted during the first and second stages of the step, then the development of activity of the newly secreted insulin must have proceeded with increasing velocity and when the concentration of the active product became sufficiently high in the tissues it rapidly became manifest and the third stage of the venous step was produced. Thus the activity develops as shown by the curve of Fig 18. It appears, therefore, that development of activity of endogenous insulin is

mented by some unknown factor Fig 3 and Fig 7 show that the venous step appears earlier on a high carbohydrate than on a high fat diet, i.e., the activity develops earlier in the former than in the latter. The similarity between these results and those obtained on the insulin depression curves is apparent, and the nature of the unknown factor as deduced from the venous step again admits various possibilities.

The increase in the A-V difference in the first stage demonstrates that there is no factor causing a lag in the removal of glucose from the blood to the cell and we are left with the possibility that the step may be produced by the burning off of an inhibitor or by the activation of insulin by some unknown factor.

An appearance similar to the venous step would be produced if a wave of inhibitor substance entered the blood soon after the taking of glucose. This conception, however, receives no support from the insulin depression curves. Assuming insulin to be in an active state when secreted, and accepting the explanations given of the first two stages of the venous step, then a more feasible adaptation of the inhibition theory is that which was applied to the insulin depression curves, namely that the inhibitor is present in greatest amount at first and is progressively removed so that insulin manifests an apparently increasing activity. If the greatest concentration of the inhibitor exists before the giving of glucose, then its greatest effect should occur in the first stage. But at this stage is found an apparent decrease in inhibition, i.e., the A-V difference increases. It may be considered, however, that although the largest amount of inhibitor is present before glucose is taken, it cannot be sufficiently large to inhibit completely the action of insulin already present in the tissues as, at this point, an A-V difference exists. Any increment of insulin will, therefore, manifest itself as an increase in the A-V difference. It is very difficult to imagine a rate of secretion of active insulin which is such that it will permit an increase in the A-V difference in the first stage, and yet in the second stage, when the inhibition is being rapidly removed, be insufficient to maintain the A-V difference in spite of the concomitant utilisation of insulin.

Although the final decision as to the presence or absence of an inhibitor must await the isolation of the activator, the above circumstantial evidence weighs against the theory of insulin inhibition. The conclusion arrived at, therefore, both from a consideration of the insulin depression curves and the venous step is that an unknown factor exists which activates insulin, the action occurring according to Fig 18.

For convenience of discussion it has been assumed that the activator acts on insulin but it will be seen that it can exert its action in at least one of three ways. It may act as an addition to insulin, it may prepare glucose for insulin action, it may activate insulin.

If it acts by addition then the third stage of the step indicates its sudden outpouring into the tissues. The arguments against the sudden secretion of insulin are equally applicable against the sudden secretion of

an activator. If it acts by preparing glucose for insulin, then this reaction must conform to the type shown in Fig 18 and although this explanation will fit the venous step it is difficult to see what stimulation would occasion the production of an activator of glucose in the insulin depression curves or why "activated glucose" being necessarily always present in the tissues, there should be any latent period after insulin injection. It is probable, therefore, that the activator acts on insulin, and the name "insulin-kinase" has been tentatively proposed for the unknown, (Himsworth (17))

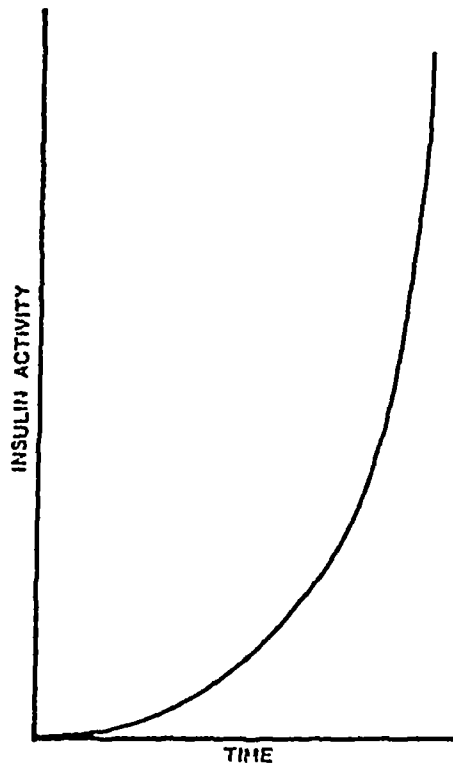


Fig 18 Curve illustrating the rate of development of insulin activity

To summarise these considerations we put forward the following hypothesis —

(1) That insulin as prepared from and as secreted by the pancreas, is an inactive substance which requires activating by insulin-kinase

(2) This reaction proceeds in an autocatalytic manner and consists of the action of this kinase on the substrate insulin

Application of the hypothesis

Reference has been made to the observation, and a confirmatory experiment described, which showed that a subject's tolerance for sugar increases after successive doses of glucose. This has usually been attributed to an increasing sensitisation of the insulin secreting mechanism. In Figs

16 and 17, however, it is shown that under these conditions there is an increased sensitivity to insulin itself, and, therefore, an increased concentration in the tissues of insulin-kinase must play some part in the progressive reduction of alimentary hyperglycaemia

The results obtained after administration of high carbohydrate diets show that more of the activator is available under these conditions than when a high fat diet is fed. The greater effect of each unit of insulin in the fasting state indicates the persistent presence in the tissues of a greater concentration of insulin-kinase. The more rapid development of the venous step signifies the more rapid production of active insulin from the islet secretion and this again points to increased kinase concentration in the tissues. And the restriction in the height and length of the hyperglycaemia curve indicates that after the step all the insulin secreted is activated at this accelerated rate.

If the total A-V difference is measured in the two types of tolerance curve, it will be found that whilst one would expect a much greater A-V difference on the high carbohydrate diet than on the high fat, they approximate very closely. In Fig 2 the area enclosed by the capillary and the venous blood sugar curves is approximately the same in both diets. As we have stated that the fundamental assumption we make is that the A-V difference is a measure of the active insulin in the tissues, these results appear to be at variance with our previous conclusions, namely, that on a high carbohydrate diet there is a greater concentration of active insulin in the tissues. On reference to Figs 11 and 12 it can be seen that very much more insulin would be required to lower the blood sugar from 50 mg/100 c c to 40 mg/100 c c than from 90 mg/100 c c to 80 mg/100 c c. It follows that very much less insulin would prevent the rise from 180 mg/100 c c to 190 mg/100 c c than from 140 mg/100 c c to 150 mg/100 c c, i.e., a much lower concentration of active insulin in the tissues will, when the blood sugar is high, produce the same effect as would a high concentration of active insulin when the blood sugar is low. Thus with a capillary blood sugar of 220 mg/100 c c an A-V difference of 30 indicates the presence in the tissues at that time of a much lower concentration of active insulin than does the same A-V difference with a blood sugar of 140 mg/100 c c. This application of the mass action theory (Himsworth (16)) gives a logical explanation of the above discrepancy.

We have deduced the persistent presence of a greater concentration of active insulin in the tissues during the period of carbohydrate feeding than when fat is fed. Thus we consider to depend primarily upon the greater concentration of activator produced. Applying the mass action theory it will readily be seen that when the blood sugar rises initially in these cases a greater A-V difference will occur. On reference to Fig 3 it will be seen that after glucose, the A-V difference shows a greater initial development on the starchy than on the fat diet.

If the resting concentration of active tissue insulin is great and, therefore, the initial increase of the A-V difference is marked, then the depletion of

tissue insulin, in the second stage of the venous step, may be small in relation to the total concentration present, with the result that the A-V difference will not diminish rapidly. Now the smaller the A-V difference in the second stage, the earlier will the onset of the third stage be detected, and, therefore, if in the second stage the A-V difference hardly diminishes, then the onset of the third stage will be masked and the venous step appear to be delayed. Thus the association of a marked initial development of the A-V difference and a delayed step on the carbohydrate regime may be expected. We have met two examples of this and Fig. 5 is the high carbohydrate tolerance curve from one. In this subject, on the high fat diet, the initial A-V difference which developed was small and the step was at 10 minutes, on the starchy diet (Fig. 5) the initial increase was well marked yet the time of the step was 35 minutes. In support of this explanation, the experiment in which glucose and insulin were given simultaneously, may be quoted (Fig. 9). Here the step was markedly delayed as compared with the ordinary tolerance curve for this subject (Fig. 6).

From a consideration of the results of feeding carbohydrate to normal subjects, it appears that by this means an increased tolerance for sugar is acquired, and similarly from the results of feeding fat, it may be concluded that a diminished tolerance for sugar is produced. These results could be explained in great part by the hypothesis that on a starchy diet more insulin-kinase is produced and on a fatty diet less of this substance is available. It has been suggested, however, that change in the pH of the blood influences the sugar tolerance markedly (Haldane and others (13)), and at first sight it would appear that on the two types of diet the pH of the blood might differ considerably. If this were found to be so then the variations in tolerance observed on the two diets might be explained on that basis. We have investigated this point and the results of these experiments will be communicated subsequently, but we may say at once that the pH of the blood is the same on both diets and that the giving of large quantities of ammonium chloride, or sodium bicarbonate over a period of seven days or more does not produce the variations in sugar tolerance or insulin action recorded in the present paper.

As there is an increased sensitivity to insulin after the subsidence of an alimentary hyperglycaemia it follows that a greater concentration of the kinase must have reached the tissues. After an insulin depression curve this increase in sensitivity has not been observed, and it thus appears that the stimulation required to produce insulin-kinase is hyperglycaemia. This increase of kinase ensures the more rapid activation of pancreatic insulin, with a resulting increase in the concentration of active insulin in the tissues. As the excess of activator persists when the curve returns to normal levels, less insulin must be secreted after the subsidence than before, for otherwise active insulin would be produced so rapidly that hypoglycaemia would result. It appears then that restriction of insulin secretion occurs with the fall of the blood sugar.

It is possible now to explain the peculiar curve with two steps shown in Fig 8. At the first step the sugar abstracted from the blood, as measured by the A-V difference, increased so rapidly that the capillary and venous sugar ceased to rise and actually fell. The stimulus of hyperglycæmia waning, the rate of secretion of insulin diminished, with concomitant underproduction of active insulin and a decrease in the A-V difference. The abstraction of sugar from the blood diminishing, hyperglycæmia again manifested itself and secretion of insulin recommenced with the ultimate production of a second step. It has been noted previously that the first step occurs about 12 minutes after the first rise began and the second step at approximately the same time after the commencement of the second rise. The appearance of Fig 9 is similar to Fig 8 and the suggested explanation is purely a combination of the explanation offered for Fig 8 and that given for the later appearance of a venous step on the high carbohydrate diet.

Although in past records of carbohydrate metabolism there are many papers concerning the effect of diet upon the sugar tolerance curve there are relatively few papers reporting the action of insulin under similar conditions. Tutso (31) showed that animals become progressively less susceptible to insulin on starvation. Abderhalden and Wertheimer (1), Bainbridge (4), have demonstrated the increased sensitivity to insulin of animals on a high carbohydrate diet. Hynd and Rotter (18) have confirmed these results and have also shown that this sensitivity is not determined by a depletion of glycogen reserves, for on a carbohydrate free diet, when the animals are most resistant, there is great depletion of liver glycogen, and on a high carbohydrate diet when they are most sensitive, the liver contains more glycogen than usual.

The conclusions derived from observations on human beings reported in this paper thus receive confirmation from the results which have been obtained on animals. In addition there have been physiological experiments which may now be interpreted to mean that some factor in carbohydrate metabolism other than insulin exists. Dann and Chambers (7) have shown in dogs that after a three weeks' fast the administration of glucose results in hyperglycæmia and glycosuria. In normal animals sugar causes a definite rise of R Q but in the starving ones the same amount of glucose produces practically no change from the resting value. Administration of 50 g of glucose on consecutive days, however, occasions a gradually increasing response until, about the fifth day, the pre-starvation rise in R Q is again observed. In an attempt to compensate for this suppression of the ability to oxidise glucose, large doses of insulin were given along with the first dose of glucose to the starved animals. A rise of R Q of normal magnitude was not obtained, relatively enormous doses of insulin could not completely restore the ability of the starved animal to deal with glucose. It appears that some other factor was missing, that this factor could be increased by the same condition which we have shown to increase the action of insulin,

namely carbohydrate feeding, and that it could be diminished by conditions which decrease the apparent activity of insulin, namely starvation, it is suggested that this missing factor is "insulin-kinase"

The most complete diminution of insulin activity produced experimentally is that reported by Markowitz, Mann and Bollmann (23). Mann and Magath (22) had shown previously that shortly after hepatectomy, insulin exerted the same effect on the blood sugar as before, but the above authors demonstrated that six to eight hours after hepatectomy, insulin may have no detectable action upon the blood sugar. They actually suggest that the action of insulin on carbohydrate in the intact animal is dependent on a third factor. In the same paper it is also shown that in a dehepatised depancreatised dog muscle glycogen is laid down only when enormous quantities of insulin are given together with sufficient glucose, but that in a partially dehepatised dog a similar quantity of glucose causes a striking increase in the glycogen content of those tissues. The authors state that although insulin does function in the dehepatised animal "its function is by no means so marked as in a diabetic but otherwise intact dog". From these experiments it appears that the unknown factor is limited in proportion as the liver tissue is diminished. We would suggest that the unknown factor is insulin-kinase and that the liver influences the development of the activity of injected insulin through being the site of production of this new substance.

It has long been recognised clinically that injury of the liver by chloroform or phosphorous may be associated with glycosuria and Opie and Alford (24) have stated that chloroform affects the liver practically exclusively. In a recent paper Althausen and Thoenes (3) have re-investigated the problem of chloroform poisoning. The experiments were carried out on rabbits and the test used was one in which water, glucose and insulin were given, the doses being such as to produce in normal animals a moderate degree of hyperglycaemia. Four stages were recognised after the poisoning with chloroform and these were correlated with the histological changes in the liver. The first stage which lasted until the end of the first 48 hours, showed a greatly increased hyperglycaemia after glucose and a gradually diminishing hyperglycaemia after adrenaline. This was associated with fatty degeneration and necrosis of the liver cells. The second stage was reached about the fifth day and lasted until about the tenth. The response to the test had become normal, the response to adrenaline had returned and, at the same time, the dead tissue was found to have disappeared from the liver and new cells were appearing. The third stage appeared from the tenth to the eighteenth day and now, after the giving of the glucose and insulin test, the blood sugar did not rise at all, but fell steadily to hypoglycaemic levels. Giving of glucose without insulin was also found to produce the same paradoxical effect. At this stage all signs of injury had disappeared and the liver was crowded with young cells. The glycogen content of the organ after the test was practically the same as in normal controls, but unfortunately muscle glycogen estimations were not made. The fourth stage was reached

after three weeks when the tolerance and response to adrenalin had again returned to normal, the young cells in the liver had matured and become arranged in an orthodox pattern. There thus appears to be a stage after injury of the liver in which alimentary hyperglycæmia is suppressed and in which this suppression cannot be accounted for by the increased capacity of the liver cells to store glycogen. This stage coincides with the period of young tissue formation in the liver and the marked increase in tolerance suggests to us an increased activity of endogenous insulin.

From the experiments of other workers, therefore, there is evidence for the existence of an unknown factor which influences the action of insulin and there is further evidence which suggests that this factor is produced in the liver.

Reference has been made to those peculiar cases of diabetes in which the patient is resistant to the action of insulin. Warren (32) has stated that "the outstanding feature of insulin resistant cases is that even complete failure of insulin production by the patient cannot explain them." In a case reported by Root (27) 840 units of insulin a day were taken for some weeks. The patient became worse and eventually, despite the administration of 1,600 units a day, died in diabetic coma. Another case, reported by Allan and Constam (2), had taken 500 units a day for some months before death. Point is lent to these cases when it is considered that the daily output of the human pancreas has been calculated to be at the most 300 units of insulin. In both the above patients post-mortem examination revealed conspicuous cirrhosis and atrophy of the liver with fibrosis of the pancreas. The most rapidly fatal type of diabetes has long been known to be that associated with simultaneous disease of the liver and pancreas, namely in hæmochromatosis. Many of these cases have now been reported as resistant to the action of insulin. Another type of case in which resistance to insulin occurs is that associated with thrombosis of the hepatic artery (Pollack and Long (25)) and consequent necrosis of the liver.

In a case seen personally the patient was under care for a surgical condition of the liver. She had no previous history of diabetes but, on admission, a trace of sugar was found in the urine. Whilst under observation, the condition gradually became worse until 140 units of insulin a day were given without controlling the glycosuria and ketonuria. An operation was eventually imperative for relief of the surgical condition but the patient died 18 hours later. A post-mortem examination was made an hour and a quarter after death. Apart from an early broncho-pneumonia there were no signs of infection. The bile ducts throughout the liver were blocked with gall stones and the organ was grossly damaged. There was no suppuration in the liver. The pancreas was macroscopically and microscopically normal, no hydropic degeneration of the cells was seen and by Bensley's method granules were demonstrable in these cells.

Thus there is definite clinical evidence to support a theory that diminution of insulin activity is associated with disease of the liver. There are experimental results pointing to the same conclusion and also evidence that

in the presence of young liver tissue the organism has an increased ability to deal with sugar. The experiments reported in the present paper demonstrate the variation of insulin activity and from the nature of endogenous and exogenous insulin action the presence of a factor which activates insulin, has been deduced. It is suggested that this factor, insulin-kinase, is produced in the liver, and an attempt is now being made to isolate this substance from that organ.

In conclusion I wish to express my gratitude to Professor C R Harington for his continued help and criticism.

SUMMARY

1 The effect of high carbohydrate and high fat diets upon (a) hyperglycaemia after ingestion of 50 g of glucose and upon (b) the rate of depression of the blood sugar after a standard dose of crystalline insulin have been investigated.

2 Simultaneous curves in capillary and venous blood have been obtained after oral administration of glucose. It has been demonstrated that, under certain specified conditions, capillary blood, obtained from the human ear, approximates closely to arterial blood in its sugar content. The sugar content of venous blood has been found to run in parallel with changes of the capillary blood sugar save at one place shortly after the commencement of hyperglycaemia. Here on the venous curve an S shaped deviation has been demonstrated. This venous deviation is brought into existence by three consecutive variations in the arteriovenous difference and the significance of each variation has been discussed. The increase in arteriovenous difference in the third variation is so marked that the venous blood sugar curve changes its direction at a sharp angle from the course previously followed. This step-like irregularity has been termed the venous step. It is concluded that this phenomenon is dependent upon the secretion of pancreatic insulin but that the latter only becomes active under the influence of an unknown factor which brings about this activation in a reaction proceeding with increasing velocity.

3 After intravenous injection of crystalline insulin it has been shown that a short latent period occurs in which there is no detectable action of insulin upon the blood sugar. This is succeeded by a period in which insulin manifests its action with increasing velocity. The duration of this latent period and the time taken for the blood sugar to reach its lowest point have been found to be independent of the dose of insulin injected. Further, results are brought forward showing that below a certain maximum dose of insulin increase in the amount of this substance injected produces a corresponding increase in the rate of fall of the blood sugar, but that above this

maximum dose no further increase in amount produces any further acceleration of depression. It is deduced from these results that the development of activity of injected insulin is dependent upon some unknown factor which activates insulin with increasing velocity.

4 In explanation of the development of the venous step and the characteristics of the depression of the blood sugar by insulin the following hypothesis is put forward —

- (a) that insulin as prepared and as secreted endogenously by the pancreas is an inactive substance,
- (b) that this substance is activated in an autocatalytic reaction with an unknown factor, and
- (c) that in this reaction the unknown factor behaves as a kinase and insulin as a substrate

5 After a period on a high carbohydrate diet the oral administration of glucose is followed by a lower and less prolonged hyperglycæmia and an earlier development of the venous step, and the injection of a standard dose of insulin is followed by a shorter latent period and a more rapid rate of fall of the blood sugar, than when the subject is taking a high fat diet. The same results are obtained when doses of glucose are given to a subject prior to investigation. It is concluded that administration of carbohydrate stimulates the production of the unknown "insulin-kinase."

6 The association of disease or injury of the liver with the development of insulin activity is discussed

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PAIN DERIVED FROM THE SKIN AND THE MECHANISM OF ITS PRODUCTION *

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THE studies that are reported in this paper arose during the progress of observations upon patients suffering from painful conditions of the skin of the feet. In attempting to determine the mechanism of pain in these patients it soon became clear that preliminary work would be needed upon normal skin. These preliminary observations form the contents of this paper.

The single quality of pain derived from superficial stimulation of the skin

It has become the custom amongst clinicians to allow patients to describe their symptoms in their own words, and to listen to their unprompted stories. This has the manifest advantage that it avoids suggesting to patients symptoms from which they are not suffering and which, if accepted in the history of the case, might affect the correctness of diagnosis. In any thorough investigation of the mechanism of symptoms, however, the importance of this procedure must not be overemphasised, and it is often necessary from this standpoint to suggest forms of description to patients, so as to obtain from different individuals statements that can be compared and related. Let us take such an important symptom as pain, and consider the forms of it as these are recognised in connection with lesions of the skin. Such pains are variously described by patients as pricking, stabbing, tearing, stinging, burning and so forth, and these and similar words pass into medical descriptions as terms defining different forms of pain that are experienced. Our first point is that for purposes of investigation these terms, which patients use, give inadequate definition and often incorporate suggestions of origin that are misleading. Clearly, most of such terms do not attempt to describe the pain itself, but refer to the agent, either that which has caused the pain, or one which is known or might be supposed to give rise to a pain having the same characteristics.

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A much more precise description of pain can be given without any great difficulty after the event but especially during the event by intelligent people provided their attention is deliberately directed to the chief characteristics of pain. Putting on one side localisation, whether this is considered from the standpoint of approximate or precise localisation, pain may be described according to its character, its duration, and its intensity, which last may vary from moment to moment. If pain is derived from skin, then localisation is usually very accurate. It is probably enough for the remaining description to consist purely of statements of intensities and of duration and to neglect characters. Thunberg (13) has distinguished a form of pain which he calls "dull" pain ("dumpf Schmerz") and which is probably derived from the deeper layers of the skin or from immediately underlying structures, such pain is readily produced by squeezing a fold of normal skin, for example the short webs of skin between adjacent fingers. If we exclude this form of pain it becomes highly probable, so it seems to us both from the published observations of Alrutz (1) and from our own observations, that all forms of pain derived from the skin are transmitted by the same nerve endings and fibres and that the "quality" or "tone" of all such pain is constant. This idea is expressed by the frequent use amongst German workers of the phrase "bright" pain ("hell Schmerz") to include most forms (*see* Frey and Rein's monograph (5)). We are unable to ascertain, however with what conviction this idea that "bright" cutaneous pain has but one quality or tone, stated as it is by Becher (2) and Alrutz (1), has been generally acknowledged, but it does not seem to have been brought, as it deserves to be if it is true, quite to the point of demonstration. To particularise the symptom pain can be provoked by injuring the skin in a large number of different ways, as by pricking with a sharp point, by pinching tiny folds of skin, by pulling on hairs, by burning, or by the passage of galvanic currents. The quality of pain produced in these several ways can in fact be demonstrated to be unvarying in that, when tests are properly safeguarded, the subject is unable to differentiate between them.

A wire of constantan 5 cm long and 0.25 mm in thickness is bent in its middle to an acute angle and suitably mounted, the wire is then heated by passing through it a current of 0.8 to 1 amp. The acute angle of the hot wire is brought into quite transient contact with the skin, alternatively the skin is simply pricked with a fine needle. A blindfolded subject cannot detect which of these two forms of stimulation is employed. Similarly, a quick tug upon a single hair or the make or break shock of a galvanic current may be employed. All these will be described by the subject as pricking pain, without distinction. Naturally, it is necessary that the subject should not be allowed to receive associated sensory (but unpainful) stimuli, peculiar to the form of stimulation. Thus, if the contact of the hot wire is maintained too long, its warmth may be felt and the form of stimulation will then be detected. When a hair is pulled, it should first be isolated so that it may be

grasped and pulled without the warning which simple contact with other hairs will give, and counter pressure should be exerted around its base so that when the hair is pulled, the skin around it is not lifted. Similar counter pressure should be exerted when needle prick, hot wire, or galvanic shock are compared with this form of stimulation. The greater the precautions taken to eliminate supplementary sensory stimuli, or to reduce these to simple uniformity in comparing different forms of painful stimulus, the more successful will be the tests. But much precaution is unnecessary, the subject tested is soon aware that it is impossible to distinguish the different pain stimuli, and that where he recognises the form of stimulation it is upon a non-painful accompanying sensation that this recognition depends.

The stimuli discussed in the last paragraph are all brief stimuli and their effects are called "pricking". A prolonged stimulus gives rise to pain described as "burning", and thus is so whether the pain arises from heat or not. The bent wire is carried just through a small cork and thus applied to the skin, and a current is now led through the wire to heat it appropriately, a needle point is sunk in a similar cork and from it a galvanic current of appropriate strength is turned into the skin, an isolated hair is pulled and held tense through a small slit in a cork held around it and in contact with the skin, or a tiny piece of skin is caught up in sharp edged forceps and pinched in similar circumstances (Thunberg). The subject cannot differentiate, all these forms of stimulus give rise to pain that is described without distinction as "burning" pain. It is described as burning pain, not primarily owing to its peculiar quality but because it is a cutaneous pain *that continues*. It is not transient, but lasts. The hot stimulus applied briefly causes what is termed "pricking" pain, prolong the stimulus and the effect is "burning" pain, the initial pull on a hair causes a "pricking" pain, but if the hair is held the quality of pain, though quite unchanged, is now called "burning". Short contacts with a test tube containing very hot water, or with a stick of solid carbon dioxide, which at once freezes the skin, are indistinguishable from each other if suitably applied (*see also* Alrutz), both give rise to a short "burning" sensation.

So far pain arising from, and ending with, very brief or short stimulation of the surface of the skin has been discussed. Pain may also continue as an after-effect of stimulation. The most widely recognised pain of this kind is the "burning" pain that continues long after contact with an object hot enough visibly to injure the skin. Pain quite indistinguishable from this arises out of injuries resulting from continued friction, from abrasions, from freezing, from ultraviolet burns and in other ways. This continuous pain, which follows as an after-effect and is common to injuries of different kinds, will be discussed at greater length presently, here it is important to note that it is identical in quality, though it is usually less in intensity, than the "burning" pain previously discussed, namely, that which occurs during the actual period of stimulation. A series of minute scratches, closely set,

gives rise after an interval of time to a very definite continuous pain, described as "burning", it has precisely the same qualities as the pain which follows as an after-effect of the injuries previously named, or which follows a prolonged application of mustard oil or of chloroform to the skin. The comparison should be made of two forms of stimulation, applied symmetrically and simultaneously to the two arms, the result is then convincing. Such observations help to substantiate the view that pain of only one *quality* can be provoked by stimulation of the skin. When we speak of pain as "smarting," "burning" or "stinging," we are using terms that lack precise distinction. Some think it convenient to say that smarting is less intense than burning, others that smarting and stinging is pain which in general begins with relative suddenness and does not long continue at full intensity. In the last instance the pain produced by the stings of insects or of plants clearly guides the definition. But the terms are in fact undefined and in ordinary parlance are largely interchangeable, what is of chief consequence is to note that when closely compared pain answering to these three descriptions cannot be differentiated in respect of quality.

In experiencing and considering pain derived from the superficial layers of the skin in response to various stimuli, we are brought more and more firmly to the belief that all such pains have but one quality, and that the variable characteristics of such pains are merely in the intensity and in the distribution in time and space.

Cutaneous pain as an after-effect of injury

We shall now describe our observations upon cutaneous pain as an after-effect of various injuries. The pain, once established, is in our experience always of long duration and of more or less uniform intensity, characters which in the case of cutaneous pain may be summed up by the popular term "burning" pain. We have worked chiefly with four forms of injury and especially with the three last of the four about to be described, as the severity of these is easiest to regulate.

1 *Burns* A convenient way of burning the skin slightly is to use molten wax. The end of a small stick of sealing wax is softened in a flame and this is pressed quickly against the previously moistened skin. After a little experience burns of suitable intensity can be produced by wax in this state (it is at about 65°C when applied) without more than slight blistering of the skin. Pain, as an after-effect of such burns may begin at once, but often there is an interval of 10 to 30 seconds or even a minute or more after the wax is withdrawn, during which there is no pain. Then gradually the pain begins, increases to its height and continues for very many minutes, an hour or more. The intensity of the pain though usually at a more or less constant level fluctuates from time to time, seeming to die quietly away and very gradually to return, but there are no sudden changes in intensity.

The more severe lesions develop tenderness and are red and swollen for hours or even days, these blister

2 *Scratching* A method of producing similar pain is to scratch the skin. An area 2 cm square is marked out on the skin, and a sharp needle point is drawn across this area ten times in parallel, ten times at right angles, and ten times obliquely. Each scratch is enough to produce a tiny white line of broken horny skin, but insufficient to draw blood. The injured region exhibits the usual vascular response, namely, reddening and whealing within 5 minutes. It is at first painless, though there may be a little itching, after 5 or 10 minutes slight "burning" pain is often felt, though this may not begin for an hour or more. Twelve hours after injury, the whole of the scratched area is usually red, swollen, tender, and burning spontaneously from time to time, and this state lasts for another whole day and sometimes longer.

3 *Freezing* An area of skin $1\frac{1}{2}$ cm square is frozen at a temperature of -18° to -12° for 20 to 25 sec, by the method described by Lewis and Love (9). Such freezes give full whealing of the skin, usually without subsequent blistering. During the half hour following the freeze the lesion itches much, itching ceases and whealing disappears in an hour or two. Within 20 hours, and often earlier, the lesion has swollen again, is tender, surrounded by a diffusion flush, as Lewis and Zotterman showed (11), and gives rise from time to time to burning pain, it remains swollen and tender for 4 or 5 days.

4 *Ultraviolet lesions* These lesions, about 2 cm square, are made by means of a mercury vapour lamp. The exposed area should be reddened, and the injury severe enough to give a conspicuous diffusion flush on the following day. Spontaneous burning pain is quite usual in such lesions within 12 hours, the lesions are swollen and tender and continue so for 5, 6 or more days, occasionally they are severe enough to blister.

The pain arising from injuries of the four kinds is always of the same type, as previously stated, and it is influenced similarly by certain interferences to be described later. The most notable variation is the early appearance of spontaneous burning pain when the skin is injured by heat and its late development in the ultraviolet burn, similar early pain may be experienced, however, after abrasions, and in very heavy freezes, which are followed by early blistering, severe burning pain occurs shortly after the skin thaws. It is impossible to state precise times that are really representative, because there is much variation with the severity of the lesion and with other factors, chief of which, as we shall see, is skin temperature.

The chief events can be introduced by illustrative but abbreviated protocols.

Min sec

- 0 0 Forearm burnt with hot wax
- 0 30 A slight burning pain of uniform intensity has developed
- 1 10 Immersion in water at 25° abolishes the pain almost completely, immersing it at 40° brings a severe burning pain within a few seconds, which decreases after a few more seconds
- 5 0 The skin is reddened and has whealed where burnt
- 8 0 The spontaneous burning pain in the skin has increased, the temperature of the lesion is 28.5° The sensory reactions to immersion at 25° and 40° are unaltered The burnt skin is noticed to be hyperalgesic
- 60 0 The pain continues in the burnt area, provided that its temperature is about 20° or above this

The pain continued to be felt for an hour or more, tenderness, swelling and redness were present next day, and a day later two small blisters appeared on the damaged skin

Time

Nov 13th

Hr min

- 12 45 A patch of skin of forearm frozen for 25 sec at -15°
- 1 45 Full whealing of the skin and widespread redness has appeared Itching has been present but has subsided There is no hyperalgesia
- 4 45 Repeated testing discovered no hyperalgesia, and immersion at 40° gave no pain
- 6 15 There is a little hyperalgesia of the skin that was frozen 5½ hours ago, it is red and "burns" a little when immersed in water at 40°
- 11 15 Tenderness has gradually increased during the last 5 hours and so has the burning pain produced by immersion at 40°
- Nov 14th
7 0 a m The damaged skin is "burning" spontaneously and continues to do so from time to time during this and the following days
- Nov 19th From the last date to this, the damaged skin has been a little swollen, very tender, deeply reddened, and surrounded by a diffusion flush The area "burns" from time to time, and "burns" much whenever immersed in water at 40°
- Nov 20th and 21st The swelling has gone, there is redness, but little tenderness, and immersion at 40° no longer gives pain

This second protocol, with small changes in the time table, would equally well illustrate the behaviour of an area of skin that has been scratched or that has been damaged by ultraviolet light The two protocols are enough to give a general idea of the events before we proceed to deal with particular features

When the skin has been damaged in any of the ways previously described, it passes sooner or later into what may be termed for convenience a "susceptible state" This will be spoken of repeatedly in this paper, it may be defined for the moment as a state of the skin, in which pain is easily induced and in which pain occurs from time to time spontaneously The susceptible state begins at varying times after injury, being delayed from a few seconds to many hours Once established it usually lasts for hours or days

Relation of pain to temperature

The simplest and most constant method of inducing pain in skin that is in the susceptible state, but in which no pain is occurring spontaneously, is to immerse it in warm water, and the temperature which experience has shown to be most suitable for general use is about 40°. In such an immersion pain starts in 2 or 3 seconds, rapidly increases to its most intense point in a second or two, when it is often severe, and then fades away, usually to disappear or to become greatly diminished at about the 7th to 10th second of immersion. In a long series of observations we have ascertained the time of onset and duration of the susceptible state, by immersing the damaged skin in water at 40° at suitably frequent intervals. Selected results are given in Table I,

TABLE I

Subject	Injury	Susceptible state		Tenderness	
		Begins	Ends	Begins	Ends
He	UV light	3½ hr	9 days	3 to 6 hr	9 to 10 days
Ho	"	4 hr	6 days	5 hr	6 days
He	"	4½ hr	8 days	4½ hr	8 days
L	"	4 hr	7 days	5 hr	9 days
L	Freeze	5½ hr	5th to 6th day	5½ hr	6th to 7th day
He	"	7 hr	4th to 5th day	7 hr	5th to 6th day
He	"	6½ hr	4th to 5th day	6½ hr	5th to 6th day
Ho	"	6 hr	—	6 hr	—
He	Scratching	5 hr	24 hr	3 hr	24 hr
L	"	15 min	48 hr	5 min	48 hr +
L	"	14 min	48 hr	28 min	48 hr
Ho	"	15 min	22 hr	15 min	24 hr +
L	Hot wire	8 min	9½ hr	95 min	—
Ho	"	20 min.	26 hr +	none	—
L	Hot wax.	½ min	4 hr +	—	—
He	Mustard oil	25 min	5 hr	25 min	4 hr
L	"	45 min	5 hr	45 min	4½ hr

which also includes other information to be used later. It will be noticed that when the skin is damaged by ultraviolet light the susceptible state does not appear for 3½ to 4½ hours, an hour or more after the skin begins to redden. It lasts from 6 to 9 days. In the case of injuries from freezing the beginning has been delayed even longer but the state lasts a few days less. Scratch injuries, and incidentally bruises, enter the susceptible state usually within 15 minutes of the injury, a much shorter time, and the state lasts 1 or 2 days. When tested, scratches should be coated thinly with vaseline, so that no water enters them. Relatively severe injuries from heat become susceptible almost at once, but by using milder stimulation, as by scattering over the area a number of minute burns with a hot thin wire, the onset of

the susceptible state can be delayed for minutes. It lasts a few hours or a day or two. Injuries arising from continuous application of mustard oil, acquire susceptibility within about a half hour, and hold it for a few hours. Immersion in water at 40° gives the same type of pain and pain lasting for much the same period of time, irrespective of the manner in which the injury has been produced.

In studying the pain that comes when susceptible skin is immersed in warm water it is important to know the temperature of the skin before its immersion, for this temperature affects the result. Thus, if in repeatedly immersing the injured skin in water at 40°, preliminary baths for 3 mins at 20° or 30° are used alternately, the pain in the test after the 30° bath is always the more intense, and often comes a second earlier and lasts a few seconds longer, than in that after the 20° bath. When the limb is transferred from 20° to 40° water the gradient of rising skin temperature is steeper than when the transference is from 30° to 40° water. But over the relevant

TABLE II

1st bath at	Copper block or 2nd bath at	Pain		
		Begins	Ends	Degree
20°	Copper 40°	sec 2	sec 11	severe
30°	" 40°	2	11	very severe
35°	" 40°	2	10	very severe
20°	" 40°	2	11	severe
30°	" 40°	2	10	very severe
35°	" 40°	2	10	very severe
30°	Bath 40°	2	8	distinct
20°	" 40°	3	8	very slight
20°	Copper 30°	—	—	none
20°	" 35°	—	—	just detected
35°	" 40°	2	9	very severe
38°	" 40°	3	7	very severe

NOTE —A given test, repeated over and over again at quick intervals (2 min. or less) does not give uniform results. The pain lessens appreciably and may disappear after as many as 10 or 20 tests. The intervals between tests should be longer (5 min.) and arranged in an order that avoids this source of error.

period of time, namely, the first 6 sec. during which pain is chiefly felt, the temperatures in the latter case are actually higher and the gradient is actually steeper for a *given* range of temperatures than in the former. The intensity of the pain in response to temperature is governed by two factors, the height of the actual temperatures and by the steepness of gradient. Thus, if the skin is transferred from water at 25° to water at 35°, from 30° to 40°, and from 32° to 42°, the intensity of the pain increases very conspicuously in this series, though the number of degrees of rise, and the rate of rise, in the three cases is not very dissimilar.

Instead of transferring the injured skin from its preliminary bath to warmer water, we may apply to its surface a large block of copper that has been allowed to lie in the warmer water. The large mass of the copper and its high conductivity of heat ensure that there is no appreciable fall of temperature for several minutes after its application. The pain then produced is much more intense, for the gradient of rise is steeper. A small quick change of temperature at a high level will suffice to produce pain that is often intense. Thus the copper block laid on injured skin at 40° after preliminary immersion at 30° , 35° and 38° respectively, produces pain of very similar intensities and durations. It is occasionally a little less in intensity in the 38° test than in the others. When pain has been induced by transferring injured skin from a bath at 30° to one at 38° or 40° and the pain has subsided, it is sufficient to move the limb in the bath, a procedure raising the surface skin temperature $\frac{1}{2}^{\circ}$ to 1° , to cause pain to return, though it does not return in its original intensity. These and other tests (illustrated by Table II) while showing that both the absolute temperatures reached and the steepness of the gradient matter, also seem to indicate that the number of degrees traversed, or perhaps more accurately the duration of the steep gradient, also plays a part.

Skin in the susceptible state can also be provoked into displaying pain by rapidly cooling it. The tests are best made by applying to the damaged skin, previously kept at 30° by immersion, a metal surface of known temperature and of such size as to affect the injured skin only, without overlapping surrounding skin. In severe ultraviolet burns an ice cold contact in these circumstances gives severe burning pain of brief duration which is abolished at once by reimmersion at 30° . Cold metal contacts at 5° , 10° and 15° also give rise to transient burning pain but less in its degree, occasionally cooling to 20° is sufficient to yield detectable pain.

Spontaneous pain and temperature Spontaneous pain occurs especially after injuries from heat but is not confined to these. It is felt from time to time in skin damaged in all the ways mentioned, provided that the injuries are relatively severe. The spontaneous pain is always continuous and uniformly of the one kind. When present it is sharply enhanced if the skin is immersed in water at 40° , but it is at once relieved or abolished by immersion in water at 25° . That pain arising from heat injuries increases with warmth and is relieved by cooling is familiar knowledge, it is less widely recognised that pain arising from any superficial cutaneous injury behaves in the same way. The knowledge that heat causes burning pain while applied to the skin, and that the pain continues subsequently in much the same form, though it may be less in intensity, gives rise to the idea that the after-effect of heat is continued in a fashion peculiar to itself. Such an idea is certainly erroneous. It would be premature as yet to discuss the mechanism of the pain, but the evidence given earlier is enough to show that the susceptible state following injuries of different kinds is a state common to them all and independent of the manner of injury.

The occurrence of spontaneous pain depends largely upon the temperature of the skin. On numerous occasions we have immersed skin that has been damaged and has become susceptible in a bath of water at about 27° or 28° and, keeping the bath well stirred, have raised its temperature at a rate of about $\frac{1}{2}$ to 1° per minute, to ascertain the lowest temperature of the skin at which pain appears. This is determined in most tests to lie between 32° and 34°. In two instances, after ascertaining the critical temperature by this method, we transferred the limb to water at this temperature from a bath several degrees lower, and found that the result was burning pain, which for a short time was more intense. Abrupt changes of this kind discover susceptibility to heat at a level 1° or 2° lower than the gradual change previously described. The critical temperatures of Table III have been ascertained in most, but not all, observations, from

TABLE III
Minimal temperature for pain

Subject	Date	Injury	Pain begins at
L	July 15	Finger hit with hammer (blood blister)	32 5°
L	Nov 15	Frozen area	32 5°
Ho	June 28	Ultraviolet burn	32 0°
L	June 22	" "	32 7°
L	July 15	" "	32 7°
L	Feb 14	" "	34 1°
Ho	July 14	" "	34 3°
Ho	Feb 7	" "	33 6°
L	Dec 23	Burn with heat, arm, one hour old, causing slight blistering subsequently	29 0°
L	Feb 22	Burn with heat, foot, one hour old, small blister	30 3°
L	—	Same as last at 3½ hours, no longer burning spontaneously	32 4°

injured skin on the dorsum of the foot, and have been obtained from subjects in the sitting posture, a posture which tends to lower the critical level. The temperatures are such as to explain why spontaneous pain is not the rule, for the temperature of the injured skin of forearm or foot only reaches the critical level from time to time in ordinary circumstances. But the temperature of the injured skin is not far below the critical level, and so the increased warmth of the skin in bed or while sitting in a well warmed room is often enough to tip the balance, and "spontaneous" pain results. Injuries resulting from heat are exceptional in that pain appears at lower levels of temperature, as exemplified in Table III, this is a form of injury in which spontaneous pain is most frequent. Injuries produced by heat are apt to be more severe than those laid down in the other ways, more frequently than with other forms of injury the damage is not so nicely graded as to be adequate without causing subsequent blistering. The severer the lesion, whatever its kind, the lower in general is the temperature first required to

induce pain, the differences in critical temperature for lesions produced by ultraviolet light or by freezing are not great unless the differences in the severity of the injury are conspicuous. It is immaterial how temperature is raised in injured skin, whether by radiant or conducted heat or by local vasodilatation, pain will result if the temperature rises high enough.

In speaking of "spontaneous" pain we mean for the moment merely pain occurring in skin that has experienced no deliberate interference such as an application of heat. As has been stated, the natural temperature of the skin may from time to time be adequate to induce pain. There are other factors, which act similarly in inducing pain, and two of these will now be considered.

Spontaneous pain and posture If the skin of the foot is injured sufficiently to render it painful at ordinary temperatures, then raising the foot to the horizontal tends to decrease or abolish the pain. Hanging the foot down determines the pain, or increases it if it is already present when the foot is horizontal. This influence of posture is not exerted indirectly through a rise of temperature, such as might be conceived to occur in injured skin when the limb hangs down. Observation shows that such a change of temperature does not occur. The pain is an indirect effect, however, and is due to stretching of the tissues by the hydrostatic increase of pressure in its vessels. Thus, the same effects can be obtained by artificially raising venous pressure in the limb that is at rest and horizontal. Whether it is the result of hanging the limb down, or of throwing a pressure of 60 or 70 mm Hg upon the veins, the pain does not appear at once but only after an interval varying from $\frac{1}{4}$ to 1 or even 2 minutes, it reaches its maximal intensity still later and gradually, the veins of the leg meanwhile having become tenser and tenser. If the leg is placed horizontally again or the obstruction to the veins is released, pain is relieved within a few seconds. The time relations of onset and offset of pain, so provoked, are obviously consistent with a purely mechanical explanation, namely, the times taken for the veins and venules to become tense or relaxed. Other things being equal, when pain is induced by raising venous pressure, the pain comes more quickly and is more intense if the temperature of the skin is higher, the vessels swell more at higher than at lower temperatures, a fact which may be in part or in whole responsible for the phenomenon just described. If burning pain has been induced in injured skin by obstructing the veins, the leg being horizontal, then occlusion of the femoral artery at Poupart's ligament quickly reduces or stops the pain. When the foot is dependent and paining, arterial occlusion has a similar effect, but the foot must usually first be flexed and extended to empty its veins before the pain is abolished. If the venous pressure has been raised and pain has developed fully, then raising the pressure to a higher point will quickly increase the pain, and lowering it a little gives quick and partial relief. If pain is present in the injured skin when the leg is dependent and in this posture only, then the direct application of pneumatic pressure to the injured skin, sufficient to counterbalance the pressure in the cutaneous

arises gradually out of the injury after a lesser or greater period of delay. It is evidently associated with the process of inflammation, being delayed until clear signs of this are established, a fact very well exemplified in the case of the delayed ultraviolet reaction. It is probably a particular and rather advanced phase of inflammation that is concerned, for the susceptible state is not developed in the early stage of redness and whealing, except in the single instance of injury by heat. There is an interesting and certainly important association with hyperalgesia, which is illustrated in Table I. If the skin is frozen, and at each subsequent half hour the damaged area is examined, hyperalgesia and a painful reaction to water at 40° are found appearing together about 5 or 7 hours after injury. A similar relation is found in the case of other forms of injury, though it may not be quite so exact. Further, hyperalgesia lasts for hours or days and the painful reaction to warmth lasts a similar though sometimes longer time. Considering that the presence or absence of hyperalgesia cannot be tested very precisely, and especially that the use of water at exactly 40° is arbitrary, perfect correspondence is not to be expected. Correspondence such as is found is far closer than can be regarded as accidental, and an obvious explanation would be that the pain nerve endings become simultaneously hypersensitive to mechanical and thermal stimulus, but that this is the relation is still a little uncertain. While the injured skin is undoubtedly hypersensitive to friction, to simple firm contacts and to the needle point, it does not seem to be so to moderate warmth and cold or to very light contacts. Rein (12) in discussing the pain threshold for heat, gives 43° as always over threshold for normal skin, and states incidentally that this threshold is lowered by chemical and mechanical stimulation of the skin, if we accept this reasonable explanation, it would be necessary to widen the statement by including lowering of threshold to painful stimuli in general. A statement that the threshold is lowered, however, is hardly more than a restatement of the facts, but the wider statement almost forces us to postulate hypersensitivity of the pain nerve endings. How this may have come will now be discussed.

CAUSE OF CUTANEOUS HYPERALGESIA AND PAIN

Chemical factor underlying hyperalgesia

The association between susceptibility of the skin to heat and hypersensitivity to mechanical stimuli has been discussed in the last paragraph and it has been concluded that both are probably the result of the same hypersensitiveness of the pain nerve endings. Now at the stage when the skin is hyperalgesic it is usually swollen, but excess of tissue fluid and tension arising therefrom is not the cause of hyperalgesia. It is usual in the case of ultraviolet burns for hyperalgesia to occur before swelling can be detected. There is no hyperalgesia in an urticaria wheal when it forms, although the tension of tissue fluids in this case is greater in the skin than in the one we are considering, but the area that has been whealed may be

tender next day and after the wheal has subsided. The hyperalgesia we are considering is not due to a simple physical cause, as the following observations show.

In relatively mild injuries the precise area damaged (scratched, frozen, or reddened by ultraviolet light as the case may be) becomes hyperalgesic. But if the injury is more severe, hyperalgesia is almost always found outside it on the day after injury and on following days. Lewis and Zotterman (11)

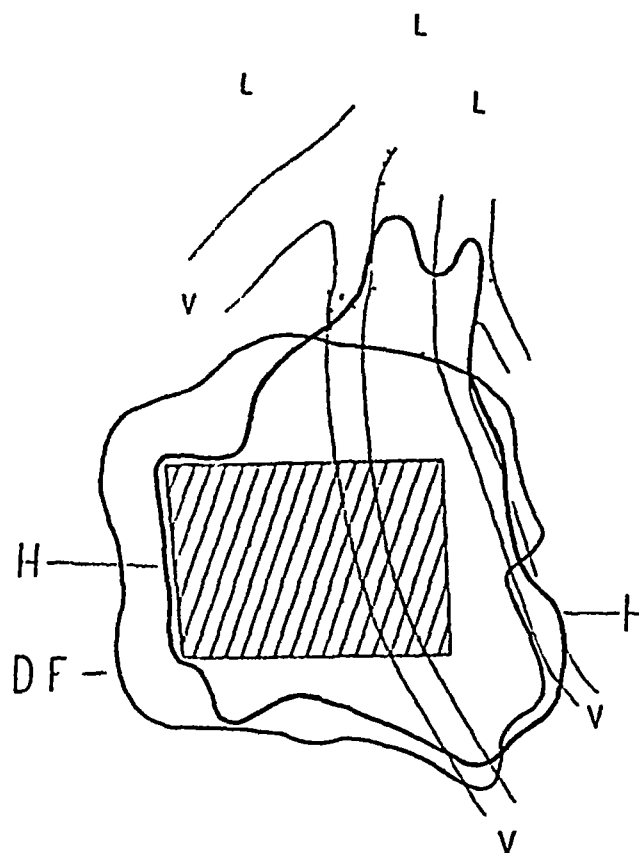


Fig. 1. L. (2/3). An ultraviolet burn has been put down over the sharply outlined shaded area (5 x 15 cm) two days previously. *DF* marks the outline of the diffusion flush. *H* the heavy line marks the limits of hyperalgesia. *V V* are the chief veins in the vicinity and the dotted lines (*L L*) mark the courses of lymphatics, over which the skin was reddened at the time. The burn was on the ventral surface of the right forearm and the proximal skin is upward in the chart.

described how an area of skin directly injured by ultraviolet light (or by freezing) becomes surrounded by a "diffusion flush," and how lymphatic channels may be marked out on the proximal side of the burn by reddened lines on the skin, they attributed these phenomena to diffusion of vasodilator substances into the uninjured from the injured skin. The fact that

hyperalgesia fails to be confined to the region actually injured suggests that it is due to chemical products of injury, which influence the pain nerve endings not only within the injured area, but also in the surrounding skin by diffusion. There is not precise, but there is approximate, correspondence between the diffusion flush area and the area of added hyperalgesia, most but not all of the flushed area is hyperalgesic but hyperalgesia often extends beyond it. Hyperalgesia often seems to follow the course of the neighbouring veins for short distances, though seldom confined to the strip of skin overlying a single vein, it is often most intense over it. In Fig 1 the area of hyperalgesia seemed related to the two chief veins of the area and the vein farthest to the right in the chart seemed to give the boundary of hyperalgesia. It is a suggestive but not very precise relation of this kind that is the rule, only exceptionally is there the clear relation of Fig 2

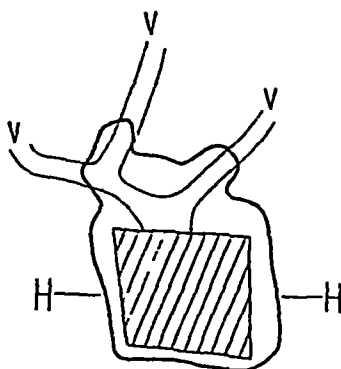


Fig 2 H ($\times 2/3$) An ultraviolet burn was put down over the area shaded (2.5×2.5 cm) two days previously. The diagram shows the relation of the area of hyperalgesia to the chief veins of the region. The burn was on the dorsum of the right foot and the upper edge of the chart is proximal.

Whether the course of veins is followed or not, it is the rule for the chief extension of hyperalgesia to be up the limb, in the direction of lymphatic drainage. These outlying areas of tenderness are not accidental and changeable, except while they are developing, they retain their distribution from day to day, tenderness of outlying areas declines simultaneously with that of the central area, in which however it lasts a day or two longer.

Chemical factor underlying pain

Pain in rubbed skin When an area of skin about 2 cm square has been damaged by criss-cross scratches, or by ultraviolet light, and this damaged skin is hyperalgesic but gives no spontaneous pain, pain may be induced in it by rubbing. We rub the skin with firm strokes of the ulnar border of the hand, using 5 strokes in 3 or 4 seconds. The skin is a little painful as it is stroked, but this does not persist more than a second or two

after the last stroke. There is a significant interval of usually 10 or 15 seconds, sometimes longer, after the strokes have ended, before pain begins, the pain grows in intensity for 15 or 45 sec declines and is gone after lasting about 1 to 3 min. There is no difficulty in repeating the observation after a few minutes of rest, and the times at which pain comes and goes, and the intensity which it reaches, are sufficiently uniform. The preliminary interval without pain, and its gradual rise to maximal intensity, are incompatible with its origin as a direct response to the rubbing, it is a delayed after effect of this act and the manner of its onset and slower decline definitely suggest that the rubbing causes the discharge of some substance into the intercellular spaces, which, first accumulating and then slowly dispersing, accounts for the curious time relations.

This idea is confirmed by observing the effects of stopping the circulation to the limb. If this is done directly before rubbing the injured skin, the pain comes as before, but it rises to greater intensity and remains at or about this intensity for as long as 3 to 7 min according to when the circulation to the limb is released. Such is a broadly accurate statement of the result. If the pain induced by rubbing is inconsiderable, it is occasionally lost during the later stages of circulatory arrest, being then overshadowed by other sensations arising in the limb, but it is rarely lost in these circumstances more than transiently, and even when it disappears it does so after a conspicuously longer time period than in the control observation with circulation free. The general effects of circulatory arrest upon this pain are indubitable, its intensity is increased and it is prolonged. When the circulation is released again the skin glows in the reactive hyperæmia, and the pain is almost always lost in this glow at once, but it frequently returns as the hyperæmia subsides about a minute after the release, and may last another half or whole minute.

The conclusion from these observations is that pain following as an after effect of rubbing is produced by a substance released into the intercellular spaces, that this substance is a relatively stable substance, and that it is diffusible, being removed when the circulation is restored.

An instance very similar to rubbing is that of stretching. If the skin is very hypersensitive, strong distension of its vessels is enough to produce pain, which however declines very quickly when the vascular pressure is relieved. Simple stretching of the skin, as has been said, produces a similar transient pain. If the stretching is vigorous, then the pain produced also subsides quickly, but within 15 or 20 sec it returns, gradually and with gathering intensity, to last perhaps for many minutes or even for hours. This pain that comes back gradually and long outlasts the physical interference, is likewise attributed to liberation of the substance, and to its acting on the pain nerve endings.

Effects of simple occlusion. If skin injured by ultraviolet light is giving rise to no spontaneous pain but is in a condition not far removed from so

doing, then simple occlusion of the circulation to the area may awaken pain in 20, 30, 60 or more seconds, this pain increases very gradually in intensity to disappear quickly when the circulation is released again. This has been shown to occur in skin damaged not only by ultraviolet light, but in other ways.

A blister had developed a day before on the palm of a hand as a result of working with a tool, the subject was just conscious of a little burning in the lesion, cutting off the circulation to this hand gradually increased the pain, which in a few minutes amounted to very unpleasant burning. On releasing the circulation this pain soon disappeared. Repetition confirmed this result.

It is apparently not unusual for diffuse but distinct burning pain to arise in the palmar surfaces of the fingers or hand during arrest of circulation to the limb, especially if the hand is kept at 34° to 35° . This will happen although there are no visible abrasions or other obvious injuries, and possibly results from small diffuse injuries associated with the hard usage to which this skin is put.

Cutaneous hyperalgesia and pain considered as a whole

In the first part of this paper observations were described to show that the same quality of pain can be produced by a variety of different forms of physical interference with the skin, such as pricking, pinching, burning, etc. The pain which is common to these different interferences is common to them because it is transmitted to the central nervous system by one nervous apparatus, that appropriate to the transmission of pain impulses. Singleness of quality does not necessarily imply any other constancy of mechanism than this. There are in fact two chief mechanisms of excitation. In one of these pain is produced at the time of the interference, in the other it follows as an after-effect. Although the pain may assume the same quality in both cases the mechanism of production is different. To exemplify, if considerable heat is momentarily applied to the skin, burning pain is felt momentarily during the application and subsides. This pain is very probably due to direct physical stimulation of the pain nerve endings by heat. But similar burning pain may continue after the source of heat is removed. This cannot be due to the direct stimulus heat, but must be attributed to a different mechanism. Transmission through the same system of nerve fibres sufficiently accounts for the similarity of the two pains.

Both Thunberg (13) and Frey (4) speculate in regard to the brief latency between a stimulus, such as a needle prick or burn and the onset of pain, and suggest that this brief latency is the result of a preliminary process, the result of products of tissue damage. These workers are speaking about the pain that occurs *during* the employment of the physical agency and not about the pain that occurs as a long delayed after-effect. It is quite possible that, as they suggest, the first pain is immediately determined by a transient

At the moment we are content to bring evidence that a pain substance is involved in inflamed skin. We have none to offer which would indicate the nature of this substance, or to suggest that it is identical with or different from the p-substance which has been shown (10) to account for pain aroused by muscles working without blood supply. It is just possible that so simple a substance as potassium is responsible, it may be that it is due to an increased hydrogen-ion concentration in the tissues, but weightier evidence will be required than that solutions of potassium salts in weak concentrations (Bommer (3)) or solutions of phosphate having a pH under 7.2 (Gaza and Brandt (6)), when introduced into the skin, produce burning pain.

Relation of itching and of burning pain

In a previous paper Lewis, Grant and Marvin (8) described how itching of the skin occurs as a result of a number of acute injuries, such as mechanical injury, burning, freezing, etc. The itch comes in the acute stage, a few minutes after the injury happens and has been attributed to the release of a substance equivalent to histamine from the damaged skin cells. The conception is that itching and the triple response are closely associated, both being the result of the same vasodilator or histamine-like substance released. Burning pain, studied in the observations here recorded, is also attributed to the action of a chemical substance and it is associated with an inflamed state of the skin. It is tempting to conclude that one substance underlies the itch, the burning pain, and the vasodilatation. But this cannot be done. Itching is very definitely a phenomenon of the acutely developing lesion, it does not occur during the development of ultraviolet reactions, it is not present as a phenomenon of the "susceptible" stage of inflammation, whether this follows mechanical injury, burning, or freezing. Itching frequently follows ultraviolet burns, but it is then very delayed, occurring after the susceptible stage has passed and when the skin is on the point of desquamating. The absence of itching in the "susceptible" stage is remarkable and seems to imply that a histamine-like substance is not, but that some other substance is, responsible for the local vasodilatation of this phase of injury reactions. The idea that more than one tissue substance may be from time to time responsible for local vasodilatation in skin injuries has been considered and discussed previously (7) and the possibility is guarded in the original definition of the H-substance, but there has not been as yet any adequate reason for believing in more than one. The idea now begins to gather more strength.

Frey appears to regard burning pain as the intensification of an itch, actually this is not the case, the very earliest sensation felt when a susceptible area is gradually warmed to the critical level has no resemblance to itch, it is interpretable as an extremely mild sensation of burning. The two sensations are distinct, throughout wide ranges of intensity, and they can only be confused when they occur, as they may, simultaneously. A clear difference in the behaviour of skin that is itching, and skin that is giving

rise to burning pain, is the reaction to warming. Itching disappears when the skin is immersed in water at 40° or 41°, the "susceptible" skin gives more intense burning pain in similar circumstances. From the mucous membrane of the nose and of the glans penis burning pain is easily provoked, but itching cannot be obtained by pricking in histamine or by injury. Perhaps itching is conveyed by nerve fibres of a special order, or by those serving the sense of touch rather than of pain.

It would be possible *a priori* to suppose that in the susceptible skin the relevant sensory nerve endings have been so changed in the reaction to histamine-like substance, that they are no longer capable of giving rise to the characteristic sensation of itching. This also can be disproved, for, if histamine (1 in 3,000 base) is punctured into an area of skin reddened and tender from ultraviolet light, it gives itching of the usual intensity. Skin so treated on the foot may give strong burning when the foot hangs down and itching only when the foot is raised, if now, the foot being raised, the skin is stretched, burning pain starts after an interval. At first itch and burn are felt together, but later the burn may be sufficiently intense to conceal the itch.

The desire to scratch an itching skin may be irresistible, and the scratching can be carried out for a time with satisfaction, but if it is repeated over and over again, there comes a time when scratching produces burning pain that lasts for minutes. The skin has entered its "susceptible" state.

There are two states of inflammation of the skin. Firstly, an acute form, which is typified by urticaria, in which the triple response is present and is accompanied by itching, in this the vascular phenomena and the itch are all ascribed to a substance closely related to or identical with histamine. Secondly, there is the "susceptible" state that develops more slowly, or that develops out of or after the first, which is typified by the ultraviolet light reaction, in this the skin is hyperalgesic and susceptible to warmth and other interferences, these giving rise to characteristic burning pain, the tenderness and the pain are due to the action of a tissue substance upon the pain nerve endings, this substance is not histamine-like though it is associated with local vasodilatation. It is possible that it is responsible for the vasodilatation, though there is no evidence of this. There is, however, suggestive evidence that in this form or phase of inflammation vasodilatation is due to a substance other than a histamine equivalent.

One other point of interest arises out of this discussion. A firm stroke of normal skin, and especially of skin prone to wheal, provokes the triple response and itching, a firm stroke or rub of "susceptible" skin, as this is here defined, provokes burning pain. Previous work has led to the conclusion that a histamine-like substance is released from the cells of the skin in the first instance, it is here concluded that a distinct substance is released from these cells in the second instance.

If these two conclusions are correct, it is still difficult to suppose that in the two instances the corresponding substance is released merely by

increase in the permeability of the same cell wall. If we were to suppose the size of the molecule of the histamine-like substance to be smaller than that of the pain substance—a suggestion which would seem to rule out potassium salt as the pain substance—then we could suppose that mild injuries would release the former only and that severer injuries would release the latter. In this way we might account for the almost immediate occurrence of long continued burning pain in the severer injuries such as arise from burns, crushes of the skin, and severe freezing. But we should still be unable to explain why the burning pain is not preceded by or mixed with itching in these instances. It is possible that release happens in some other way, in one or other case, or is from cells of different types. Further information is required before further discussion along these lines can be undertaken profitably.

Clinical application

The observations recorded in this paper were suggested exclusively by similar observations previously undertaken upon patients suffering from various conditions, in which the skin of the feet was reddened and tender. The observations here recorded upon skin of normal subjects, deliberately inflamed by artificial means, are first described because this order of description is the simpler and more convenient. It is clear, however, from what has already been done on patients that there are several or many clinical conditions, in which the skin of the foot is reddened and painful, and that this skin is in the same susceptible state as that described in this paper. Patients having severe erythrocyanosis of the feet, those suffering from severe and chronic chilblain, some of those suffering from thromboangiitis obliterans—and this list is not exhaustive—complain of burning pain in the feet, which is aggravated by warmth, by dependency, and by friction, and is relieved by cold, by the horizontal position, and by immobility. These symptoms are not symptoms peculiar to a specific disease, which might be termed “erythromelalgia,” they are subjective manifestations of a certain state of the affected skin. This state has here been called the “susceptible state”, it is probably associated with a given phase of inflammation, and due to the presence of a tissue substance which, playing on the terminal nervous apparatus subserving pain, renders the nerve elements hypersensitive to stimulation, or in suitable circumstances stirs in them the transmission of pain impulses. As soon as this correlation between a group of symptoms and the common underlying factor is grasped and this knowledge is applied to clinical cases, then we are able to examine and to think about cases hitherto passing by such diagnostic names as “erythromelalgia” from a fresh point of view, which at once gives a much closer understanding of these cases. Those parts of the present studies which deal with patients are progressing upon the basis here clearly indicated, and will, so it is hoped, be the subject of a separate but later report.

CHIEF CONCLUSIONS

1 Apart from "dull" pain, such as is said to arise from its deeper layers, the skin is capable of giving rise to pain of one quality only. Different types of pain, such as "pricking" or "burning," result chiefly from differences in duration.

2 Skin that is sufficiently injured in any way enters sooner or later a "susceptible" state, in which the pain nerve endings are in a hypersensitive state so that the skin is hyperalgesic and its pain threshold to heat is lowered.

3 Skin in the susceptible state usually displays spontaneous burning pain when its temperature surpasses 32° to 34°C , it may do so at lower temperatures.

4 Venous congestion, produced by dependence or otherwise, often causes pain from skin in the susceptible state. This is due to stretching of the skin by engorgement of vessels.

5 The "susceptible" state is not the immediate result of injury but of ensuing inflammation. It is caused by the liberation of some tissue substance, which acts on the pain nerve endings.

6 When skin in the "susceptible" state is rubbed, pain appears as a delayed after effect. This pain is caused by the further liberation of the same tissue substance, the concentration of which now rises to a level adequate to produce pain. Simple occlusion of the circulation may similarly raise the concentration of the substance in damaged skin to the adequate level.

7 The excitation of pain nerve endings arising during actual stimulation of the skin is probably physical or physico-chemical, the mechanism is quite distinct from that which produces pain as a delayed after-effect of stimulation and which is here studied.

8 Itching and pain are distinct phenomena, the first is associated especially with the triple response and the latter with a later stage, or more delayed form, of inflammatory reaction.

9 Suggestive evidence is put forward that the vasodilatation accompanying the latter type of inflammatory reaction is not due to a histamine-like substance, but to some other vasodilator substance.

10 The state of susceptibility described, and occurring for example in the extremities, is often accompanied by burning pain which is aggravated by warmth, dependency, and friction, and which is relieved by cold, the horizontal posture, and immobility. These symptoms are not those of a specific disease, which might be termed erythromelalgia, but are due to a state of the skin which is common to a number of separate clinical conditions.

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CLINICAL OBSERVATIONS ON TWO PURE GLUCOSIDES OF DIGITALIS, DIGOXIN AND DIGITALINUM VERUM *

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THE drugs of the digitalis series have attracted exceptional interest during the present century because of their unique position in the treatment of heart disease. Attention has been devoted largely to the pharmacological and clinical study of the mixed active principles of the different plants as they occur in the leaves or seeds or simple extracts. The isolation and characterisation of the active glucosides have presented chemical problems of no little difficulty, and few, as yet, have been proved to be pure chemical compounds. Crystalline g-strophanthin (ouabain), which is derived from *strophanthus gratus*, has established its claim to be considered a chemical entity, and is used as the international standard for biological standardisation of other preparations of strophanthus. In digitalis leaves, several glucosides are present in varying amounts. Some are ill defined chemical bodies, it is still doubtful whether even digitoxin has been isolated in a chemically pure state. Little is known of their effects in man, and our scanty knowledge provides a situation not unlike that which would arise, if we knew much about the clinical use of hyoscyamus, and but little of the action of hyoscyamine, atropine and hyoscyne, its constituent alkaloids. In the case of digitalis, an attempt is made to secure the uniform activity in man of different samples of leaf and tincture by biological standardisation on animals, the drugs being given parenterally. These methods take into account neither variations in the rate of absorption of the different constituent glucosides from the alimentary canal, nor variations in their rate of elimination from the body. It is not surprising, therefore, that there are on record cases, in which tinctures of similar potency on biological assay, have given widely differing clinical effects (Wedd (17), Hatcher (5), Eggleston (3)).

The clinical study of the pure separated glucosides of digitalis is thus of interest, not only in distinguishing their different properties, but also because it affords the possibility of obtaining standard preparations which

* A report to the Therapeutic Trials Committee of the Medical Research Council. Specimens of digoxin, digitalinum verum and standardised ouabain, together with the results of biological standardisation of the new drugs, were obtained from Messrs Burroughs Wellcome & Co, through the Therapeutic Trials Committee.

can be given in known doses without biological standardisation. This paper is devoted to the study of two such substances, digoxin and digitalinum verum.

A new pure crystalline glucoside has recently been isolated by Smith (15) from the leaves of *Digitalis lanata*. It has the empirical formula $C_{41}H_{64}O_{14}$, and has received the name digoxin. Biological tests show that it is a very potent member of the digitalis group of drugs. Smith and Grant (16) have re-examined digitalinum verum, a glucoside present in the seeds of *Digitalis purpurea*, originally described by Schmiedeberg (14), and further studied by Khan (8) and Windaus, Bohne and Schwieger (18). They have found that the purest "digitalin" of previous workers is not a homogeneous substance, but consists of digitalinum verum mixed with four other glucosides. They have succeeded in isolating chemically pure digitalinum verum, which is thus available for the first time for clinical investigation.

Method

General considerations. The activity in man of a drug of the digitalis group may be shown in several ways. In both healthy and diseased hearts it may produce changes in the length of the *P-R* interval, or in the form of the *T* wave in the electrocardiogram. If it is given to a patient suffering from congestive cardiac failure, the breathlessness may be relieved, and the signs of increased venous pressure, such as the enlarged liver and the over-filled veins in the neck, may diminish and finally disappear. If oedema is present, it may vanish with a concomitant increase in the output of urine and diminution in the body weight. Though it is said to be sometimes possible to demonstrate these signs of improvement in congestive failure, when the heart is beating with normal sinus rhythm, it is in cases where the auricles are fibrillating that they may be confidently anticipated. In this condition, they are constantly associated with, and can be attributed mainly to, a fall in the ventricular rate. Enquiry into the activity of a new drug of this class is thus directed, in the first instance, towards its capacity to diminish the rate of the heart in cases of auricular fibrillation, and it is immaterial whether these cases show, in addition, the signs of congestive cardiac failure. If the results of increased venous pressure are present, attention is directed towards them with the realisation that they are essentially secondary effects.

When a drug is given by mouth, it may be altered or destroyed during its passage along the alimentary canal, its absorption may be incomplete in degree and variable in rate, it may produce local effects. For these reasons, and especially because of the more rapid response obtained, intra-venous injection is preferable for testing a new drug. A fuller study will include administration by mouth when evidence of potency has been obtained. Finally, it is useful to compare the effects and dosage of a new substance with those of a well established drug of the same type.

These general considerations have led to the method adopted in the investigation of digoxin and digitalinum verum which will now be described in detail

Selection of cases Digitalis was withheld for a fortnight from several outpatients with auricular fibrillation, and those who showed a substantial rise in ventricular rate were admitted to hospital. Those with chronic bronchitis and considerable cardiac enlargement were found to be unsuitable. The bouts of coughing associated with chronic bronchitis produce erratic variations in ventricular rate, those who had considerable cardiac enlargement tended to develop severe congestive failure which demanded immediate treatment.

Details of method Patients chosen for investigation were allowed to rest in bed until ventricular rates taken at corresponding times of day for several days were approximately the same. Tests with one of the glucosides were then begun. Ventricular rates were taken electrocardiographically every 10 to 15 minutes from about 9.0 a.m. for at least an hour. In most cases, the ventricular beats were counted directly on the screen, in some, the rates were subsequently read off from electrocardiograms. When three consecutive readings were in good agreement, one of the new drugs was injected intravenously. Further readings were taken at intervals of 5 minutes for the first half hour, and at intervals of 10 to 15 minutes for the next two hours. At this point the patient was usually given lunch, and further readings were taken during the afternoon. The anticipated effective doses of the new glucosides were calculated on the basis of the biological standardisation. A fifth of this amount was given intravenously in the first observation on each drug, and the amount was then increased until definite effects were produced. Several days were allowed to elapse between successive injections to avoid the effects of cumulation. Injections of amounts finally decided upon as effective doses were repeated, thus each of the two glucosides was injected twice, and sometimes three times in each case. The effects were then compared with those of a standard sample of ouabain given intravenously. The new drugs were given in dilute (8% and 9%) alcoholic solution, and 20 c.c. of a simple solution of alcohol (8%) were given intravenously as a control. No alteration in rate was observed during the short time after injection of alcohol alone when an effect might possibly have been evident, and observations were continued to determine the normal variations in ventricular rate throughout the day. Lastly, each case was brought under the influence of digoxin administered by mouth. A large dose was given at about 10.0 a.m., and the case was followed through the day in the same way as in the intravenous tests. Further smaller doses were given in the evening and on the next and subsequent days, and the heart rate was counted by auscultation over the impulse at four or more standard times each day. When the dose was known which would maintain the heart rate at a low and steady level from day to day, digoxin was replaced by

standard tincture of digitalis, and the dose was adjusted until the same rates were recorded.

This complete investigation was carried out in three cases. The method is laborious, but this is inevitable if strict clinical comparisons are to be made. Other therapeutic procedures have to be suspended for a long time, it is not, therefore, a suitable method for the study of cases with a degree of congestive failure greater than is relieved by an initial period of rest in bed. Similar results having been obtained from each of the three cases, the alcoholic control and ouabain injections were omitted in subsequent tests, in these, three cases received digoxin and digitalinum verum intravenously and digoxin and tincture of digitalis by mouth. Digoxin was also given orally to several cases unsuited for full investigation of the intravenous effects. Where congestive failure was present, notes were made in all the cases, of the venous pressure as estimated by the excess filling of the veins in the neck, and often of the urinary output with a constant fluid intake.

The results obtained with each drug will now be recorded in detail.

Digoxin

Digoxin, the crystalline glucoside derived from the leaves of *digitalis lanata*, is very insoluble in water, but dissolves more easily in dilute alcohol. A solution containing 0.5 mg. of the glucoside in each c.c. of 80% alcohol was used for intravenous injection. An amount containing the desired dose was withdrawn from a rubber capped bottle and mixed in the syringe with nine times its volume of sterile saline so that the injected fluid contained 8% alcohol. The solution was then slowly injected into a vein in the forearm over a period of three to five minutes. The glucoside is very irritant, and care must be taken to avoid any leakage into the tissues outside the vein. For oral administration, a solution containing 0.5 mg. digoxin in 1 c.c. of 80% alcohol was used, freshly diluted with water, or with chloroform water, which helps to cover the bitter taste of the solution. Comparison with the effect of international standard digitalis leaf on the frog shows that 0.6 mg. digoxin is equivalent to 1 c.c. of standard tincture of digitalis. In the cat 0.1 mg. of digoxin has the same effect as 0.1 mg. of standard ouabain, or 1 c.c. of standard tincture of digitalis. The doses given in the first few observations were based on these figures.

The effect of intravenous administration on the ventricular rate. Digoxin has been given intravenously in 8% alcohol to nine cases. Single doses of less than 0.5 mg. had little effect, single doses of from 0.75 mg. to 1.0 mg. caused a rapid and considerable fall in the ventricular rate. The fall began five to ten minutes after the midpoint of the injection, was rapid during the first half hour, and reached its full extent after one to two hours. The rate rose after lunch and tea, in some patients more than in others, but maintained, until the evening, a level lower than in the control period before the injection. A rise in ventricular rate after meals is usual in auricular

fibrillation, and was found to be greater when the patients were followed through the day without the injection of an active drug. The average rate on the day following the injection of 0.9 to 1.0 mg digoxin was a little lower than on the day preceding it, but after from 48 to 64 hours no effect on the rate could be detected. Control injections showed that 20 c.c. of 9% alcohol had no appreciable effect on the rate. Fig. 1 shows a typical result.

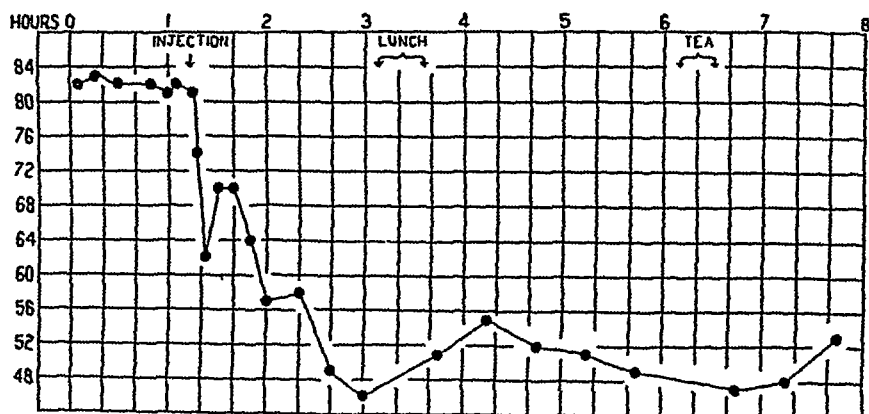


Fig. 1 The effect on the ventricular rate in auricular fibrillation of 0.9 mg of digoxin given intravenously (Case 3)

after the injection of 0.9 mg of digoxin. The full fall in rate after this dose is usually about 30 beats per minute, but it varies a little from case to case, and is greater when the initial rate is high. The activity of digoxin was compared in three cases with that of 0.25 mg ouabain which had 90% of the activity of USP X standard ouabain issued by the US Dept of Agriculture. 1.0 mg of digoxin had a slightly greater effect than this dose of ouabain, clinically, it is a little more potent than biological standardisation suggests. Details of the comparison are given in Table I.

The effect of oral administration on the ventricular rate. Thirteen cases of auricular fibrillation received single doses of 1.0 to 2.0 mg of digoxin by mouth. A rapid reduction in the ventricular rate took place in every case. The fall began an hour after the drug had been given, and reached its full extent in six to seven hours. The initial rates and the rates at these times are given in Table II, while Fig. 2 shows in detail the rate of fall in Case 8, in which a high initial rate prevailed. Six hours after the first dose, smaller doses of 0.5 to 1.0 mg a day were given, until a full therapeutic effect was obtained, and rates* of between 50 and 60 were recorded. The dose was next determined which would maintain the ventricular rate at a constant average daily level (usually between 60 and 70) over a period of a week or

* The rates throughout this paper refer to ventricular beats per minute

TABLE I

The effect of intravenous injections of digoxin, digitalinum verum, ouabain and alcohol (control) on the ventricular rate in three cases of auricular fibrillation which received all three drugs

	Drug	Dose in mg.	Average rates in ventricular beats per minute				
			One hour before injection	First half hour after injection	Second half hour after injection	Second hour after injection	During after noon
CASE 3.	Digitalinum verum	3.0	86	78	74	73	81
	Digitalinum verum	5.0	90	71	74	74	75
	Digitalinum verum	5.0	90	70	69	64	64
	Digoxin	0.9	85	69	52	52	55
	Digoxin	0.9	83	68	59	50	54
	Ouabain	0.25	82	65	60	59	73
	Control 20 c.c. 8% alcohol		77	73	76	81	74
CASE 5.	Digitalinum verum	2.5	110	95	94	93	99
	Digitalinum verum	5.0	111	72	71	81	100
	Digitalinum verum	5.0	101	86	81	81	96
	Digoxin	0.5	104	93	92	89	97
	Digoxin	1.0	108	87	85	87	92
	Ouabain	0.25	109	94	87	88	97
	Control 20 c.c. 8% alcohol		91	87	86	88	95
CASE 6.	Digitalinum verum	3.5	80	72	65	66	80
	Digitalinum verum	5.0	90	73	74	72	72
	Digoxin	0.75	80	71	66	67	73
	Digoxin	1.0	98	80	70	67	67
	Ouabain	0.25	95	87	78	76	77
	Control 20 c.c. 8% alcohol		80	78	77	77	83

more. Finally, digoxin was replaced by standard tincture of digitalis, and the dose was adjusted until the average daily rates were the same as under digoxin. The daily maintenance doses of the two drugs are given in Table II, the average for digoxin is 0.50 mg. a day, and for standard tincture of digitalis, 2 c.c. a day. The time taken for the ventricular rate to return to its initial level after a single dose of 1.0 to 1.5 mg. was found to be three days. When

PURE DIGITALIS GLUCOSIDES

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TABLE II
The effect of doses of digoxin by mouth in cases of auricular fibrillation

Case	Sex	Age	Etiology *	Congestive Failure	Dose in mg	Ventricular rate			Nausea—Vomiting—V.	Daily maintenance dose		Oral dose digoxin in mg equivalent to 1.0 mg intra-venously
						Before	One hour after	Six to seven hours after		Digoxin in mg	Tincture of digitalis in cc	
1	M	66	Indef	Present	1.5	90	80	72		0.60	2.5	2.0
2	F	19	Rh	Present	1.0	140		92		0.60	2.0	
3	M	31	Rh	Absent	1.0	88	77	62		0.50	1.25	1.5
4	F	44	Rh	Present	1.0	124		81		0.50	2.75	
5	M	47	Indef M S	Absent	1.5	88	73	62		0.25	2.0	1.75
6	M	41	Indef	Absent	1.5	88	80	71		0.50		2.25
7	F	50	Indef	Slight	1.0	140	121	88	N	0.50	2.0	1.5
8	M	36	Rh	Present	1.5	115	99	86	N V	0.50	2.5	2.5
9	M	41	Rh	Present	1.25	96	80	77		0.25	2.0	
10	F	40	Rh	Present	1.25	96	88	70				
11	F	37	Rh	Present	1.0	100	140	110	V			
12	F	31	Rh	Present	0.75 intra-venously	140	105	82	V	0.35	1.25	
13	M	55	Rh	Absent	1.25	91	84	64	V			
14	M	50	Indef M S	Present	1.25	140		96		0.60	2.5	

* Rh—Cases giving a definite history of acute rheumatism
Indef, M S—Cases with no history of acute rheumatism but with mitral stenosis present

Indef—Etiology unknown and probably degenerative

the rate had been reduced to 50 or 60, five to seven days were required for complete elimination. This short time before the rate rises again after its administration has ceased, and the high daily maintenance dose, suggest that digoxin is fairly rapidly eliminated from the body.

In six cases the response to intravenous injections of digoxin was known, and the extent of absorption could be roughly estimated. The total dose of

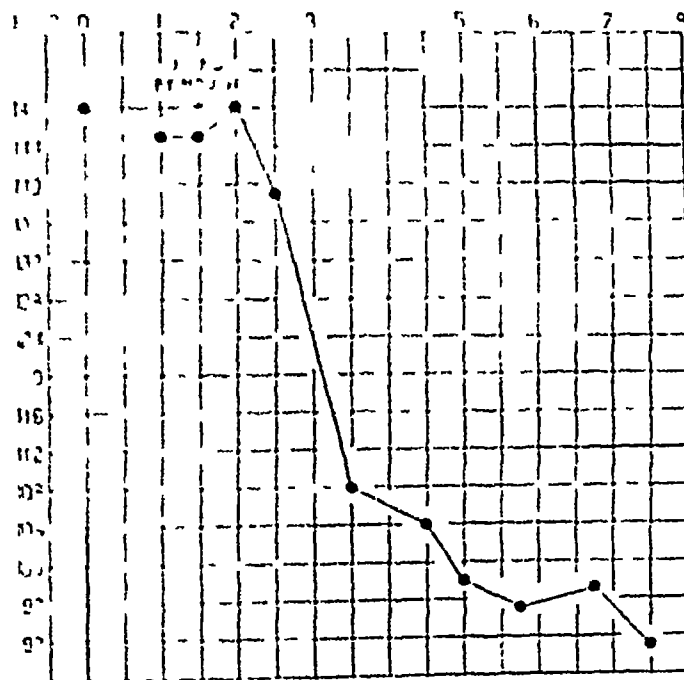


Fig. 2 The effect on the ventricular rate in auricular fibrillation of a single dose of 1.5 mg digoxin given by mouth (Case 8)

digoxin by mouth (*i.e.*, the initial large dose plus the smaller doses given over the next 12 to 24 hours) which gave the same fall in ventricular rate as 1.0 mg intravenously is given in Table II. It will be seen that a dose of 1.0 mg intravenously and 1.5 mg orally give much the same effects when allowance has been made for the amount eliminated during the longer period over which it was given by mouth. This comparison, and the speed with which the ventricular rate begins to fall after a dose by mouth, show that digoxin is rapidly and fairly completely absorbed from the alimentary canal. It is more rapidly absorbed and more rapidly eliminated than digitalis, and this explains why it is possible to obtain a definite effect on the ventricular rate with a dose only two to three times the daily maintenance dose. It differs, too, from digitoxin in these respects, for Eggleston (2) showed that this drug is a little less rapidly absorbed than digitalis.

The occurrence of nausea and vomiting after digoxin. All the active drugs of the digitalis series cause nausea and vomiting when given in

sufficient amounts, and, as Cushny (1) points out, any drug which does not, is unlikely to act on the heart

Nausea and vomiting were observed in only one case after intravenous administration of digoxin. This patient had severe congestive failure with 9 cm excess filling in the veins in the neck, and had vomited once during the six hours before the drug was given. At 12 30 p m when the ventricular rate was 146, 0.75 mg of digoxin was injected intravenously. The rates taken at 1 30, 2 0, 3 0, 4 0 and 5 0 p m were 105, 94, 86, 82 and 82 respectively, and over this period of time the patient vomited four times. A further dose of 0.17 mg was given at 7 0 p m, and further doses of 0.34 mg a day for eleven days. Although the ventricular rate sank to 52 in three days and was maintained at a low level, no further vomiting occurred.

Digoxin, given by mouth to two other patients with severe failure who were vomiting, was followed by a similar temporary increase in the severity of the vomiting during the time when the ventricular rate was rapidly falling. Further doses were given, leading to a greater reduction in rate, but the vomiting ceased. One patient vomited 2 hours after 1.25 mg of digoxin by mouth, but not after one drachm of tincture of digitalis, which had much less effect on the ventricular rate. Of the remaining ten cases who received digoxin by mouth in single doses of 1.0 to 1.5 mg, one experienced temporary nausea, the others noticed no gastric symptoms. Two of these patients, however, vomited after several weeks' treatment, when the apex rate had fallen to between 50 and 60, in both, tincture of digitalis also caused vomiting when subsequently given in doses sufficient to reproduce these rates.

The mechanism of vomiting brought about by drugs of the digitalis series has received much attention and the available facts have been collected by Hatcher and Weiss (6). The evidence suggests that it is due to a reflex from the heart and not to a direct irritant action of the drugs on the stomach. It is probable that in all the cases in which vomiting occurred after digoxin, it was due to such an effect after absorption. In the case to which it was given intravenously, and in those which received a single large dose by mouth, there was an interval of one to two hours between the time when the drug was given and the onset of vomiting. At this time, a rapid fall in the ventricular rate was taking place. Nausea was experienced in half an hour to an hour by 10% of the cases to which Robinson (13) gave single large doses of tincture of digitalis. Vomiting appears to be produced by digoxin neither more nor less easily than by digitalis when the two are given comparably.

Other effects of digoxin. Ten of the cases of auricular fibrillation treated with digoxin had congestive failure. In all of them the excess filling of the veins in the neck diminished after the ventricular rate had been reduced, and in eight cases it subsequently disappeared. In two cases in which the venous pressure remained raised in spite of full slowing of the heart, digoxin was replaced by digitalis, but this, too, had no effect on the failure.

A restricted and known fluid intake was given to five cases of auricular fibrillation showing congestive failure with œdema, and the urinary output was measured. In all these cases, a diuresis was recorded on the day following 1.0 to 1.5 mg. by mouth, and this was maintained in four of the cases when smaller doses were subsequently given. As the urinary output increased, the œdema diminished and finally disappeared.

It is well known that substances belonging to the digitalis group will cause alterations in the form of the *T* wave in the electrocardiogram if they are given in sufficient doses. Pardee (11) and many American observers believe that the therapeutic effect of digitalis is always accompanied by flattening or inversion of the *T* wave, which can, therefore, be used to test the activity of a drug of the series. Other observers have not been able to confirm this view (Grünbaum (1), Winternitz (19)). It must be remembered that the alterations in cardiac rate, which occur after these drugs in cases of auricular fibrillation, may themselves give rise to changes in the form of the *T* wave. Records from two cases showed diminution in the amplitude of the *T* wave in lead III, beginning 1 and 1½ hours respectively, after intravenous administration of digoxin. In two cases single doses of 1.5 mg. digoxin by mouth had no effect on the *T* wave, although definite slowing of the heart was produced. In one case, 5.5 mg. given orally over 4 days, and in another, 8 mg., given over 10 days, diminished the amplitude of the *T* wave in lead III.

Two cases, whilst under treatment with digoxin, developed numerous extrasystoles when the rate had fallen to between 60 and 70, and one case showed coupled beats at a ventricular rate of 40. The administration of digoxin was stopped, and after several days, when extrasystoles had become much less frequent, tincture of digitalis was given. In each of these cases, when corresponding rates had been reached under treatment with digitalis, the same abnormalities were recorded as after digoxin.

Digitalinum verum

Digitalinum verum, the glucoside obtained from the seeds of *digitalis purpurea* is more soluble than digoxin in dilute alcohol. A solution in sealed ampoules, containing 2.5 mg. in 5.0 c.c. of 9% alcohol, was used for intravenous injection, and one containing 1 mg. in 1 c.c. of 9% alcohol, for oral administration. Comparison with the effect of international standard digitalis leaf on the frog showed that 2.5 mg. digitalinum verum is equivalent to 1 c.c. of tincture of digitalis. In the cat, 1.0 mg. of digitalinum verum has the same effect as 0.1 mg. of standard ouabain or 1 c.c. of standard tincture of digitalis.

Effect of intravenous administration on the ventricular rate For safety, the dose of digitalinum verum given in the first few injections was based on the smaller figure provided by biological standardisation. Doses less than 2.0 mg. were found to have no effect on the ventricular rate. Eight cases

then received one or more injections of digitalinum verum in doses of 2.5 to 5.0 mg. The smaller quantities had a small but definite effect on the rate, the larger produced a considerable fall in every case. As with digoxin, the fall began in from four to five minutes after the midpoint of the injection, and reached its maximum in one to two hours. The effect of 5.0 mg. usually passed off in 24 to 48 hours. Fig. 3 shows a typical result from this dose.

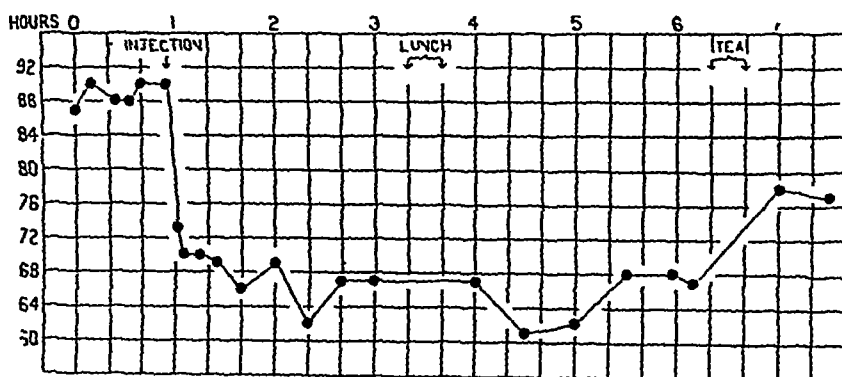


Fig. 3 The effect on the ventricular rate in auricular fibrillation of 5.0 mg. of digitalinum verum given intravenously (Case 3)

It will be seen that the fall in rate is less than that produced by 0.9 mg. digoxin in the same case (Fig. 1). In the other five cases to which both drugs were given intravenously, it was found that 1.0 mg. of digoxin had a slightly greater effect than the 5.0 mg. of digitalinum verum. Its activity was compared in four cases with that of ouabain of 90% standard activity, and 5.0 mg. of digitalinum verum had an equal or slightly less effect than 0.25 mg. of ouabain. Details of the comparison of digitalinum verum, digoxin, and ouabain in three cases are given in Table I.

Other effects of intravenous administration of digitalinum verum. No patient complained of nausea, vomiting, abdominal pain or diarrhoea after receiving 5.0 mg. of digitalinum verum intravenously. Cases showing more than a slight degree of congestive failure were not treated with this drug, but in two with slight failure there was an increase in the urinary output in the 24 hours following the injection of 5.0 mg. Diminution in the amplitude of the T wave in lead III was found in the electrocardiograms from two cases out of four from which they were taken, occurring first 1½ and 4 hours respectively after the injection of 5.0 mg.

Effect of oral administration of digitalinum verum. In 1893 the impure digitalinum verum then available was given orally by Pfaff (12) to 16 patients, including several with cardiac failure, in doses of from 6 to 9 mg. a day. He noted clinical improvement, and a diuretic effect greater than that of digitalis. A year later Khngenberg (9) failed to confirm these results. He gave as much as 20 mg. a day for several days to a number of cases without

any effect on the pulse rate or urinary flow, although both were profoundly affected by subsequent doses of digitalis. About twenty years later, Eggleston (2) found it necessary to give 18 mg a day for more than 4 days to one case to obtain a full therapeutic effect, whereas, in another case, only a sixth of this quantity was necessary.

The pure digitalinum verum at our disposal was given by mouth to four cases of auricular fibrillation. Two cases received totals of 30 mg and 40 mg respectively, distributed over two days, the other two received totals of 60 mg and 70 mg respectively, distributed over three days. In none could any significant changes in the ventricular rate be detected. Three of these cases were known to respond fully to 5.0 mg doses of the drug given intravenously, and all reacted subsequently to digoxin by mouth. In one, the T wave in lead III of the electrocardiogram, which had been diminished in amplitude by 5.0 mg digitalinum verum intravenously, remained unaltered after 60 mg by mouth. It seems certain that less than 5.0 mg of the drug was absorbed from these large doses. All four patients complained of diffuse abdominal pain and tenderness on the day after the second or third dose, two had, in addition, colic and diarrhoea persisting for two days. It has been known since the time of Withering that diarrhoea and colic may occasionally arise after large doses of digitalis. Cushman (1) and Hatcher and Eggleston (7) state that these symptoms are brought about in the same way as vomiting by an action of the nervous system rather than by local irritation of the bowel. Yet the absence of diarrhoea after digitalis was noted by Mckenzie (10) in a series of 13 cases, although vomiting was frequently produced. On the other hand, strophanthus and squills frequently gave rise to diarrhoea, often without greatly affecting the heart rate and without producing vomiting. The symptoms of irritation of the large intestine after oral administration of digitalinum verum in the above four cases arose without any signs of its absorption. When pain and diarrhoea arise after any drug of the digitalis series has been given by mouth it seems probable that irritation of the bowel by unabsorbed glucosides, or by substances produced from them either by bacterial or digestive action, is as in the above instance responsible. In considering the cause of the diarrhoea which occasionally arises after large doses of digitalis, it must not be forgotten that both the leaves and their simple extracts contain other substances than the readily absorbed digitoxin. They contain substances such as "digitalein," which are only absorbed with difficulty, and purgation is more reasonably attributed to those than to an assumed central effect of the digitoxin.

The difference in ease of absorption of digoxin and digitalinum verum is the reverse of what would be expected from their relative solubilities in water. This phenomenon is common among the digitalis glucosides. A very large dose of the water soluble strophanthus has to be given by mouth to produce the same effect on the heart as a small dose of digitoxin, which is very insoluble in water.

Suggestions for the therapeutic use of digoxin and digitalinum verum

It is usually unnecessary to give digitalis preparations directly into the blood stream. Suitable cases are those in which the ventricular rate is high and signs of congestive failure seem urgent. It is an especially appropriate method for cases which vomit immediately anything is introduced into the stomach. The drawback attending the intravenous use of most of the existing preparations is the inconstant activity of different samples of the same drug. The potency of some preparations, like strophanthum, diminish with time. Different samples of digitalinum verum and digoxin have given uniform results, and the strength is undiminished after being stored for several months. It must be remembered that it is unwise to give any preparation of digitalis intravenously to a patient who has already been receiving digitalis during the preceding fortnight. With this precaution, a dose of 50 mg digitalinum verum may safely be given intravenously to an adult of average weight. This dose reduces the ventricular rate considerably within an hour of its administration. A dose of 0.75 to 1.0 mg of digoxin, given intravenously, will produce a similar result. It has the advantage over digitalinum verum that its administration can be continued by mouth, the first dose being given 4 to 6 hours after the intravenous dose.

Digoxin and digitalinum verum were examined to see if they were suitable for subcutaneous injection. Small amounts of each, either dissolved in dilute alcohol or suspended in saline, were injected into the writer's forearm. Both glucosides gave rise to pain and swelling at the site of the injection. Digoxin is more irritant than the same amount of digitalinum verum, but the relatively large dose of the latter required to produce any effect on the heart, precludes its subcutaneous administration.

The rapidity with which digoxin acts, when given by mouth, makes it unnecessary to resort to injection save in exceptional cases, such as those who are vomiting. A single dose of 1.5 mg should be given by mouth to an adult weighing 65 kg (140 lbs) or over, if it is certain that he has not recently received a drug of the digitalis group. The dose should be 1.0 mg to 1.25 mg in lighter patients, or in those who have been under digitalis therapy during the preceding fortnight. After 6 hours further doses of 0.25 mg should be given every 6 hours until the ventricular rate lies between 60 and 70. The dose which will maintain this level should then be found, this averages 0.50 mg a day and is best given in divided doses. The maintenance dose may be given indefinitely and one of our patients has been taking a daily dose of 0.75 mg for over 7 months.

To sum up, digoxin is a very potent glucoside of the digitalis group, giving rapid and consistent effects both by mouth and when injected intravenously. It should prove of much value in the treatment of cardiac cases. Digitalinum verum on the other hand is inert when given by mouth, and its usefulness is restricted to cases where a rapid effect by intravenous injection is required. Thus digoxin is distinctly the more useful of the two glucosides.

SUMMARY

1 The effects of digoxin, a new, pure, crystalline glucoside, derived from the leaves of *digitalis lanata*, and of chemically pure digitalinum verum, isolated from the seeds of *digitalis purpurea*, on cases of auricular fibrillation have been fully and systematically investigated

2 Five to ten minutes after 0.75 to 1.0 mg of digoxin have been given intravenously, ventricular slowing begins and is maximal in 1 to 2 hours. An intravenous dose of 1.0 mg digoxin causes a fall in rate slightly greater than that observed after intravenous injection of 0.25 mg of ouabain of 90% standard activity

3 A similar, but slightly less reduction in ventricular rate, takes place after intravenous injection of 5.0 mg of digitalinum verum

4 Digoxin, given by mouth in single doses of 1.0 to 1.5 mg, causes a rapid fall in ventricular rate, beginning one hour after its administration, and reaching its full extent in six to seven hours. Digoxin is absorbed and is eliminated more rapidly than digitalis, and if sufficient is given, it causes vomiting which, like vomiting after digitalis, is produced centrally

5 In patients suffering from congestive cardiac failure and auricular fibrillation, the degree of congestion diminishes after treatment with digoxin. When a diuresis is present, diuresis occurs

6 Digitalinum verum, given by mouth in doses of 30 to 70 mg over two to three days, has no effect on the ventricular rate, but gives rise to abdominal discomfort and diarrhoea. These gastrointestinal symptoms are caused by direct action on the bowel

7 It is suggested that digoxin and digitalinum verum, as pure and stable glucosides of the digitalis group, requiring no biological standardisation, are useful drugs in the treatment of auricular fibrillation when rapid effects are desired. Digoxin can be given both by mouth and intravenously. The usefulness of digitalinum verum is limited, since it only produces its effects on the heart when given intravenously

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OBSERVATIONS ON THE MECHANISM OF HEADACHE PRODUCED BY HISTAMINE *

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HEADACHE is a prominent complaint in many grave disorders of the cranial contents, and, in a milder form, the occasional or frequent experience of most healthy people. Yet in no condition is the nature of the disturbance resulting in headache understood, many suggestions have been made, but supporting evidence has been meagre. It is still uncertain whether headaches arising in the course of different diseases are or are not fundamentally the same.

Progress would be recorded, if the mechanism of even one variety of headache could be determined. In headaches occurring naturally in disease the problem offers unusual difficulty, for, since the events precipitating the pain are so often unknown, it is rarely possible to work under controlled conditions. When our interest in the subject began, we observed, what others have noted before, that the injection of histamine is often followed by severe headache. Since this headache can easily be produced in normal subjects under conditions that may be varied at will, it offers great practical advantages for study, and the following is an account of observations made to elucidate its mechanism.

Method

The severity and duration of the headache produced by histamine depend on two factors, the dose entering the circulation in a given time, and the susceptibility of the subject. To enable us to control the quantity entering the circulation we have always injected histamine intravenously. As a single injection, we have found 0.1 mg. of histamine acid phosphate† to be the most suitable dose for 70 kg. adult subjects. The most constant

* Work undertaken on behalf of the Medical Research Council. A preliminary account was published in *Brit. Med. J.* 1932, ii, 1097.

† All doses of histamine in this paper are expressed in mg. of the acid phosphate.

results are obtained when this is given rapidly, which can be best effected by injecting 0.1 c.c. of a 1 in 1,000 solution in sterile saline. The headaches described in this paper have, unless otherwise stated, been produced in this way.

The intensity of headache developed in response to a given dose of histamine varies in different subjects, and in the same subject from day to day, the cause of this variation in susceptibility is obscure. On a single day a single subject usually behaves fairly constantly to histamine given in similar circumstances, provided that a sufficient time interval (20 or more minutes) elapses between successive injections. Because of the day to day variation in susceptibility, every observation to test the effect of a modifying factor on the headache has been preceded and followed by a control.

The subjects used have been chiefly healthy adult males. Some observations have necessarily been made on patients,* and the results obtained on them differ in no important particulars from those on healthy individuals. Patients with meningitis, cerebral tumour or arterial hypertension, and those suspected of a disturbance in the circulation of cerebrospinal fluid have been excluded. In each observation the subject has been at rest and, unless otherwise stated, lying down. No special precautions have been taken respecting the time of day or incidence of meals, since these have not been found to influence susceptibility. Each observation has been made on at least three subjects, some of whom were ignorant of the experiences of the remainder. Each subject was informed he was going to have an injection which might give him a headache. He was told to state when headache began, when it ceased to get worse, when it started to get better, and when it disappeared. On the basis of these statements diagrams of the intensity of the headache have been incorporated in the figures illustrating this paper. No attempt has been made to portray minor changes in the intensity of the pain.

The headache after intravenous injection of 0.1 mg. histamine acid phosphate

The action of histamine on the systemic circulation begins about 20 seconds after its intravenous injection, and is signalled by a metallic taste in the mouth and by flushing of the face. About 20 seconds after the taste, a sense of throbbing fullness is felt in the head. About 40 seconds after the taste headache begins and, rapidly increasing, reaches a maximum about 30 seconds later, it remains maximal for a further minute, or minute and a half, and then lessens, finally disappearing 6 to 10 minutes after the injection. The ache occurs at first in isolated throbs synchronous with the temporal pulse, but, as it increases in severity, it becomes continuous with throbbing exacerbations. As time passes, throbbing becomes less conspicuous, and the intensity of the pain is unaffected by the pulse beat in the last 3 to 4

* I or allowing us to make observations upon these patients while under their care, we wish to thank Professor Elliott, Dr. Walsh, Dr. Blake Pritchard, Mr. Trotter and Mr. Taylor.

minutes of its course. What is here described as headache is a definitely painful sensation to be carefully distinguished from the sense of discomfort which usually precedes it. The severity of the pain is variable but may be so great as to give rise to restlessness. The time relations of the headache just described are those which we have found to be typical for susceptible normal subjects after doses of 0.1 mg. With smaller doses, or with less susceptible subjects, the headache is less severe, begins later, and ends earlier. The converse is true with increased dosage or susceptibility. Rarely, a remnant of headache may last for several hours.

In normal subjects the ache always affects both sides of the head equally. It usually begins in the forehead, often just above the orbits, occasionally in the temples, and, while remaining maximal there, invades the vertex and occasionally the occipital region as it increases in severity. As the ache lessens, the area involved retreats until, finally, it is restricted to that initially affected. The pain is a little dull in character, hard to locate precisely and is felt deep in the head. It is unaccompanied by tenderness of the scalp. Nausea is unusual but may be experienced when the headache is severe; vomiting has occurred only twice in over two hundred observations. Bright spots in front of the eyes have been described by Best and McHenry (2), but have not been experienced by any of the subjects examined by us.

THE PLACE IN WHICH HEADACHE ARISES

The disturbance producing headache may, conceivably, take place in the scalp, the skull or the cranial cavity. It will first be shown that the headache does not arise from the scalp.

The circulation to the scalp is arrested by pneumatic pressure applied, around the calvarium, along a line passing just above the supraorbital crests and mastoid processes. On exerting a pressure a few mm. above systolic blood pressure, the scalp remains blanched until the release when it flushes vividly; the pressure should be such that it produces little discomfort. If histamine is injected intravenously, about half a minute after arresting the circulation to the scalp, headache develops in the usual way.

If, after a histamine headache has developed, the head is rapidly shaken from side to side, or is nodded, the severity of the pain is greatly increased. The effect appears a fraction of a second after shaking begins and gradually subsides a few seconds after shaking ends. Shaking the head will bring back a headache that has just disappeared at rest, but has no effect before, or long after, the injection of histamine. It must be supposed that the disturbance producing headache arises in a structure which is strained when the head is shaken. This structure cannot be the calvarium; it probably lies in the meninges since the brain will tend to oscillate independently of its rigid case, and so strain these membranes.

Further evidence as to the anatomical origin of the headache is obtained by studying the effects of nerve section. Histamine has been given to 3 patients in whom sensation over the cutaneous distribution of the

which is richly supplied by nerves. There seems to be agreement that mechanical stimulation of the meninges only produces pain, when the parts in the immediate neighbourhood of the large arteries are disturbed. It is to be noted, however, that the structures responding to faradism and to clamping may not be free pain nerve endings, they may be the nerve fibres.

THE NATURE OF THE DISTURBANCE PRODUCING HEADACHE

It has been suggested by Leake, Loevenhart and Muehlberger (14) that cerebral vasodilatation may be a factor in the production of headache, on the grounds that nitroglycerine dilates the cerebral vessels in animals and may produce headache in man. The more recent observations of Forbes, Wolff and their collaborators (10), (26), (28) on the pial circulation have shown that a number of agents, said to produce headache in man, also dilate the cerebral vessels. But these headaches have never been adequately described, and the facts are too meagre to warrant any conclusions as to the mechanism of such pain. It is known that in man histamine acts chiefly on the vascular system, and it is possible that the headache may result from this action. To investigate this possibility, we have determined the relationship between the development of headache and the physical changes due to the action of histamine on the vessels.

The events following intravenous injection of 0.1 mg histamine acid phosphate

The events following the intravenous injection of 0.1 mg histamine are summarised in Fig. 1*. About 20 seconds after the injection, and simultaneously with flushing of the face, the pulse quickens, the blood pressure falls, and the cerebrospinal fluid pressure rises. The facial flush rapidly deepens, is maximal 20 to 40 seconds after its onset, and then slowly fades, lasting in all about 3 minutes. The curve of cerebrospinal fluid pressure runs nearly parallel to the intensity of the facial flush. The fall of arterial pressure is of shorter duration. The relationship of the headache to the changes in arterial and cerebrospinal fluid pressures will now be described in detail.

The arterial blood pressure† The effect of histamine on the arterial blood pressure has been variously described by previous workers. Thus after subcutaneous injection of 1 mg Harmer and Harris (11) found a fall in systolic and diastolic pressure the rule, while 42 out of 50 patients observed by Weiss, Robb and Ellis (25) are said to have responded to intravenous injection of 0.001 mg histamine per kg body weight by no change, or a rise

* To ensure accuracy we have confined our attention to the headache and not more than two of the physical changes in each observation. The interrelationship of the different events is, however, remarkably constant after the rapid injection of a given dose of histamine.

† Measurements of arterial blood pressure here described were made by the auscultatory method below a Riva Rocci armlet.

of 15 mm Hg. In all of our observations (50 on 10 subjects) the intravenous injection of 0.1 mg histamine has produced a fall of blood pressure, the fall in systolic pressure has varied from 10 to 35 mm Hg and in diastolic pressure from 10 to 10 mm Hg. The fall of diastolic is usually a little

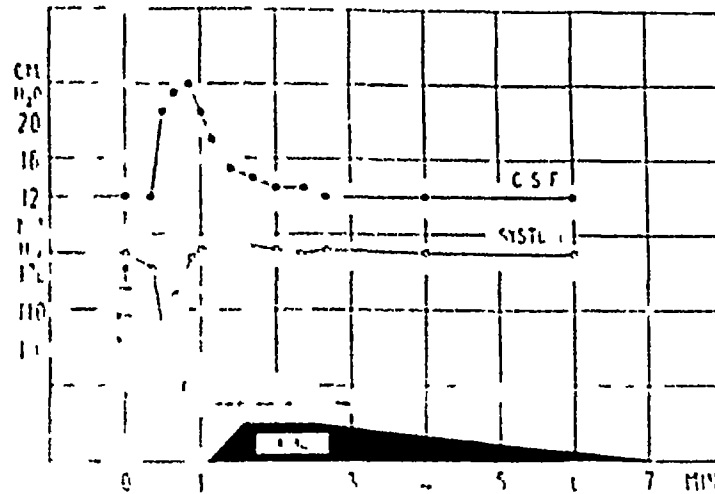


Fig. 1 To show the course of the cerebrospinal fluid pressure (CSF), the systolic blood pressure, the facial flush (hatched area) and the headache, after the intravenous injection of 0.1 mg histamine acid phosphate at 0 minutes. The values for cerebrospinal fluid pressure and systolic blood pressure represent the average of 10 observations on 6 subjects, and 10 observations on 5 subjects respectively. The course of the facial flush and of the headache represent 15 observations on 6 subjects. The intensities of the headache and of the flush are represented approximately. In this and subsequent figures the times when headache begins (can't get work), starts to lessen, and disappears have been charted. These points have been joined by straight lines.

greater than that of systolic pressure, as Fig. 2, typically, shows. Coincident with or shortly before the taste, systolic and diastolic pressures fall sharply, attain their lower limit 5 to 10 seconds later, and then more slowly return to their resting values. The fall of systolic pressure usually lasts 30 to 40 seconds, the fall of diastolic is detectable a little longer. It is usual for the systolic, and not infrequent for the diastolic, pressures to be raised by 5 to 10 mm Hg during the 30 to 60 seconds after recovering from their fall.

Headache has never been noted to occur during the period of lowered systolic blood pressure, it begins a few seconds after this has regained its normal level. While the headache is increasing in severity the blood pressure is usually a little raised, but during the remainder of the course of the headache the blood pressure is normal.

*The lumbar cerebrospinal fluid pressure.** In 16 patients lumbar puncture was performed in the horizontal position for diagnostic purposes.

* Measured in the observations here described in a vertical manometer tube attached to the upright limb of a 3 way tap incorporated in the lumbar puncture needle.

and the changes in cerebrospinal fluid were related to the development of headache after the intravenous injection of histamine. The results are summarised in Fig 1 and Table I. The cerebrospinal fluid pressure begins to rise at the moment the face flushes, reaches a peak value 5 to 30 seconds later and then begins slowly to fall to its resting level, which is reached about 2 minutes from the outset. Headache does not begin until the cerebrospinal fluid pressure is falling from its highest value, it increases in severity as the pressure returns to its resting level, but its further course is not associated

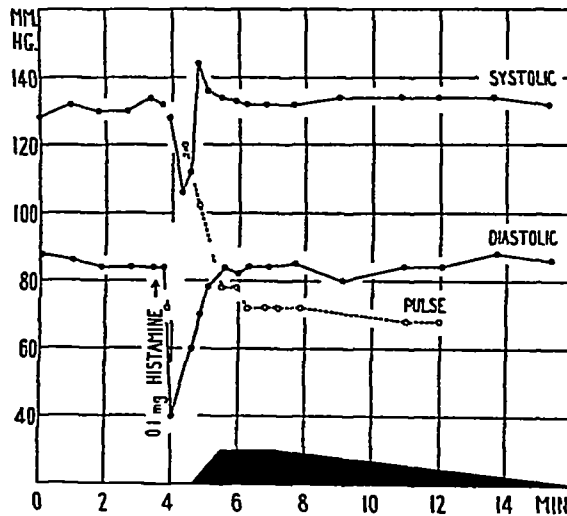


Fig 2 Ho Jan. 17th, 1933 Shows the course of systolic and diastolic blood pressure, of the pulse rate (in beats per min), and of the headache, in response to an intravenous injection of 0.1 mg histamine acid phosphate. The pulse rate was counted at the wrist in 10 second periods.

with any change in lumbar pressure. The height to which a given dose of histamine raises the lumbar pressure has varied in different subjects, 0.1 mg causing a rise of from 3 to 23 cm of cerebrospinal fluid, but the magnitude of this rise in different subjects presents no constant relationship to the intensity of the succeeding headache.

The intracranial pressure. In 3 patients presenting cranial defects from craniotomy for subdural cyst, bullet wound of the brain, and section of sensory root of the trigeminal nerve, we have observed the changes in intracranial pressure transmitted through the soft tissues overlying the aperture in the skull. To avoid leakage in the recording system a small rubber balloon was inflated inside a capsule of dental wax modelled to fit the margins of the bony defect. The neck of the balloon passing through a hole in the capsule was connected to a recording tambour writing on smoked paper. The subject was sitting to avoid the respiratory changes in intracranial pressure which appear in the horizontal posture.

TABLE I

To show the time relations of the rise of lumbar pressure and of the headache after the intravenous injection of histamine acid phosphate. The order of these cases is approximately that of the severity of the headache.

Diagnosis	Sex Age	Dose injected	Time after injection					Max rise of pressure
			Rise of lumbar pressure			Headache		
			begins	max	ends	begins	ends	
		mg.	min sec	min sec	min sec	min sec	min sec	cm CSF
1 Diarrhea colitis	F 29	0.12 0.07	0 15 0 14	0 37 0 44	1 10 2 20	1 0 1 13	17 0 30 0	5 6
2 Diarrhea colitis	F 50	0.10 0.10	0 28 0 21	0 43 0 40	2 13 2 6	1 38 1 16	12 0 —	21 14
3 Diarrhea colitis	M 17	0.12 0.07*	0 28 0 20	0 41 0 52	2 18 2 12	0 55 1 13	0 0 6 0	23 9
4 Diarrhea colitis	M 46	0.08	0 19	0 49	2 15	0 55	8 0	20
5 Polymyositis	F 43	0.08	0 20	0 25	2 53	0 35	8 0	18
6 Diarrhea colitis	M 56	0.11 0.11	0 17 0 17	0 37 0 45	2 10 —	0 57 0 48	4 0 —	13 17
7 Anterior poliomyelitis	M 29	0.10	0 27	0 40	1 15	1 25	14 0	4
8 Tabes	F 60	0.10 0.10 0.10*	0 25 0 20 0 23	1 0 0 55 0 30	2 55 2 5 2 15	1 50 1 17 0 45	3 20 7 0 7 40	22 15 5
9 Progressive muscular atrophy	M 60	0.10*	0 25	1 5	—	1 10	—	6½
10 Sarcoid	M 46	0.10*	0 15	0 40	2 6	1 15	5 40	12
11 Polymyositis	M 28	0.10* 0.12	0 16 0 25	0 26 0 47	2 15 2 15	1 35 1 15	4 40 4 0	3½ 5
12 Brachial neuritis	F 57	0.10	0 17	0 48	2 50	1 03	2 15	23
13 Disseminated sclerosis	M 26	0.10	0 12	0 45	1 45	1 35	2 10	18
14 Progressive muscular atrophy	M 41	0.10* 0.10	0 25 0 25	0 43 0 45	3 8 —	none 1 0	— —	6 5½
15 Osteoarthritis	M 52	0.11*	0 23	0 50	2 0	none	—	5½
16 Brachial neuritis	F 34	0.08	0 13	0 25	1 30	none	—	15

* After withdrawing 5 c.c. cerebrospinal fluid, except in cases 3 and 8 where 15 and 10 c.c. respectively were removed.

The changes in intracranial pressure so recorded are similar to those of the lumbar cerebrospinal fluid pressure already described. Thus, coincident with the flush and taste, intracranial pressure begins to rise sharply, quickly reaches a peak and then more slowly returns to its resting level, the total duration of the rise after 0.1 to 0.12 mg histamine being 70 to 120 seconds. The relationship of the headache to these pressure changes is illustrated by a typical example in Fig. 3 and is similar to that described for lumbar cerebrospinal fluid pressure. Headache does not begin until the pressure is falling from its peak value, and reaches its maximum severity and subsequently continues when the intracranial pressure is at or about its resting level. The rise in lumbar pressure in response to histamine has been recently noted by Weiss, Robb and Ellis (25), who, failing to find any

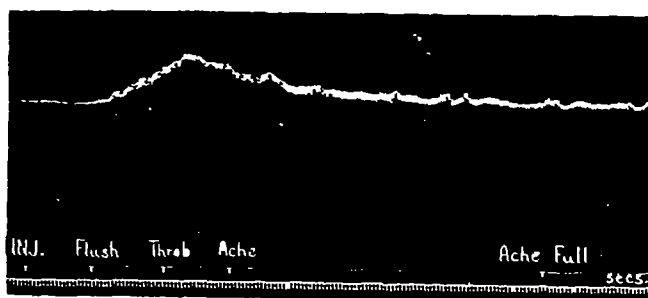


Fig. 3. Go. Craniotomy 6 cm diameter in temporo parietal region following operation for subdural cyst. August 18th, 1932. A record of intracranial pressure by the method described in the text. At INJ. 0.12 mg histamine acid phosphate was injected intravenously. The headache began 37 seconds, was at its height 1 min. 20 secs, and disappeared 7 minutes after the appearance of the facial flush.

appreciable change in systemic venous pressure, ascribed it to cerebral vasodilatation. Thus they confirmed in a patient whose brain was exposed under ether anaesthesia, for they observed that intravenous injection of 0.05 to 0.1 mg histamine acid phosphate produced flushing, bulging and increased pulsation of the brain, changes lasting 90 to 120 seconds. In cats under amytal anaesthesia, Forbes, Wolff and Cobb (10) observed the pia mater through a glass window screwed in the skull, they found that the intravenous injection of 0.003 to 0.47 mg histamine per kg body weight dilated all the pial vessels from arteries 288 μ in diameter to those of capillary size. These workers also showed that Lee's (15) failure to observe cerebral vasodilatation from histamine was due to the vessels being already maximally dilated by the ether, employed as anaesthetic. Lastly, Keller (13) has observed with Rein's thermostromuhr on dogs under pernakton anaesthesia that intravenous injection of 0.05 to 0.2 mg histamine produces a large increase in bloodflow through the carotid artery, in spite of a coincident fall of blood pressure. Thus, it is certain that histamine produces cerebral

vasodilatation. Because the rise in lumbar pressure lasts so short a time, and because it is unaccompanied by significant changes in general venous pressure it is probably due to cerebral vasodilatation alone. While the rise in lumbar and intracranial pressures must be ascribed to expansion of the vessels of the central nervous system, their fall may be due in part to an increased absorption of fluid tending to restore the normal pressure level. When the rigidity of the craniospinal space is reduced by the absence of part of the cranial vault, this compensatory process takes place only slowly, as will be shown later. The fall of intracranial pressure as recorded in Fig 3, therefore represents mainly a narrowing of the vessels of the brain, a conclusion which is supported by the similarity between the duration of the cerebral flush observed by Weiss, Robb and Ellis (25) and the rise in pressure here described. Thus we may say that after an intravenous injection of 0.1 mg histamine, headache develops as expansion of the cerebral vessels, taken as a whole, subsides. This conclusion harmonises with the observation that pain begins and increases in severity as the facial flush fades.

The striking fact that emerges from these observations is that headache does not occur while the physical changes due to vasodilatation are most intense, it develops as these subside. This relationship is not accidental, as the following observations on prolonged infusions and repeated injections show.

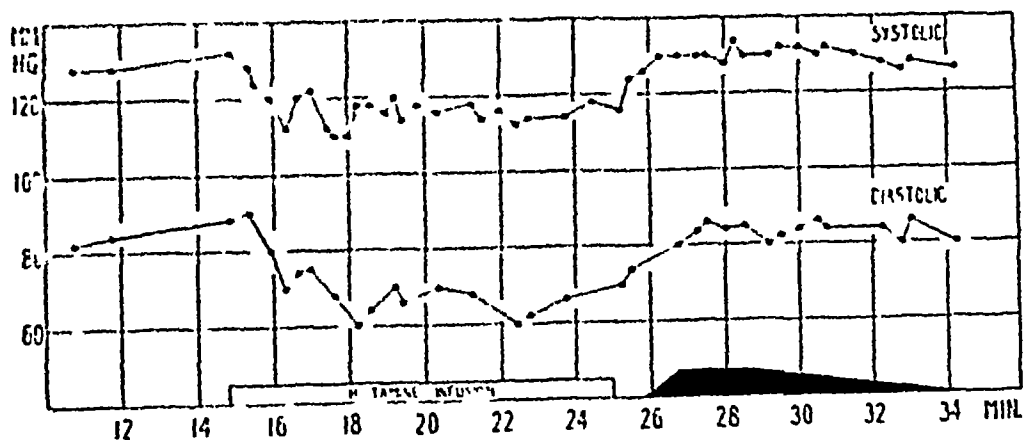


Fig 1 K Aug. 11th, 1932. Shows the course of systolic and diastolic blood pressures and of the headache in response to an intravenous infusion of histamine at the rate of 0.13 mg per minute.

The intravenous infusion of histamine at a constant rate

The ten subjects examined by us may be divided into two groups, according to their behaviour to histamine infused intravenously at a steady rate of 0.1 to 0.17 mg per min. In the first group of 8 subjects who experienced no headache during the injection of histamine, lowered systolic and diastolic blood pressures were recorded throughout the infusion, in

each of the 6 subjects in whom blood pressure was measured (Fig 4) About 30 sec after stopping the infusion the pressures rose to their resting levels, and often in the next minute a little higher

The lumbar cerebrospinal fluid pressure, examined in 2 cases, showed an initial sharp rise, which was not maintained, the pressure gradually subsiding to its resting level, which was reached about 8 minutes from the outset (Fig 5) After stopping the infusion the lumbar pressure slowly sank to a level below that from which it started Intracranial pressure recorded on two occasions from a cranial defect also fell from its highest point during the infusion, but the fall was less rapid than that of lumbar

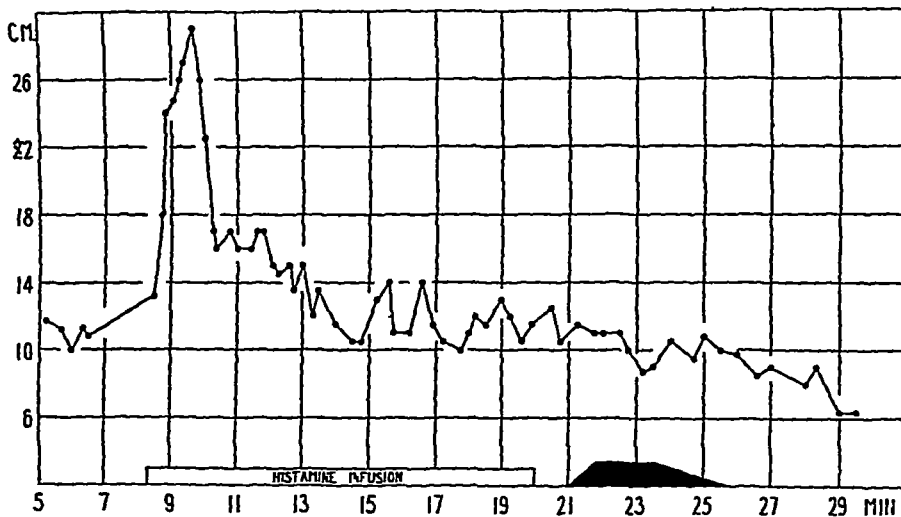


Fig 5 Ma (Painful appendectomy scar) Aug 10th, 1932 Shows the course of the lumbar cerebrospinal fluid pressure and of the headache in response to an infusion of histamine at the rate of 0.15 mg per minute In this and subsequent figures the lumbar pressure is in cm of cerebrospinal fluid

pressure and 10 minutes from the outset was still incomplete (Fig 6) The subsidence of lumbar and intracranial pressures, during the infusion of histamine at a steady rate, might be due either to a decline of cerebral vasodilatation or to increased absorption of cerebrospinal fluid That the second is the correct explanation was concluded by Weiss, Robb and Ellis (25), who first described the phenomenon, because they found that, although the lumbar pressure fell to its resting level during the infusion, the pulse oscillations remained increased Thus we have been unable constantly to confirm, but we agree with their conclusion for the following reasons In the first place there is no evidence that dilatation of the minute vessels subsides during the infusion, for the flush does not fade from the face, and the forearm volume, recorded plethysmographically, remains increased Secondly it is known that raising the cerebrospinal fluid pressure, without a corresponding rise of pressure in the dural venous sinuses, increases the rate of

absorption of cerebrospinal fluid until its pressure again approaches the normal level. That the fall of intracranial pressure during the infusion shown in Fig. 6 is less pronounced than that of lumbar pressure in Fig. 5 is probably due to a difference in the rigidity of the craniospinal spaces occasioned by the large opening in the cranial vault of the subject of Fig. 6.

In all the 8 subjects of this first group no headache developed during infusions lasting for 1, 8 or 10 minutes, the only sensation experienced in the head was of throbbing fullness during the first 2 to 4 minutes, although after the 6th or 7th minute a trace of headache could be produced by quickly shaking the head. This tendency to headache, during the later stages of the infusion, may be correlated with the subsidence of raised intracranial pressure. In all of these subjects headache began 30 to 70 seconds after

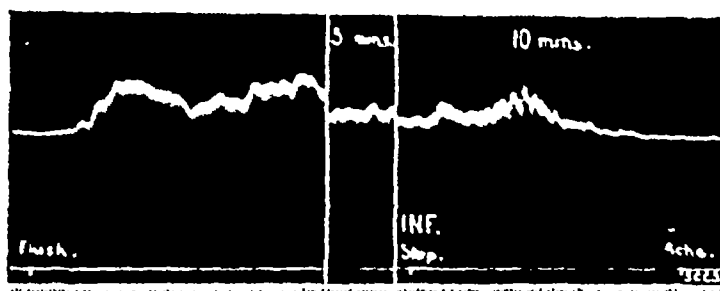


Fig. 6. Go. Au. 14th, 1912. Shows the curve of intracranial pressure from the same subject as of Fig. 7. An infusion of histamine at the rate of 0.1 mg. per minute was commenced 10 seconds before the flush signalled in the figure. The curves at 5 minutes and at 10 minutes after beginning the infusion are shown. The infusion was stopped at 10 minutes. Headache began at 11 mins. 10 secs and lasted 3 minutes.

stopping the infusion, no matter what its previous duration, the pain quickly reached a maximum and then declined, lasting 3 to 6 minutes in all. The headache was similar to, but rather less severe than, that produced by a single injection of 0.1 mg. In all of these subjects the onset of headache coincided with, or quickly followed, the recovery of the arterial blood pressure from its fall.

Two features distinguished the second group of two subjects. In the first place, both subjects developed severe headache during the course of the infusion, 1 minute and 4 minutes, respectively, after the onset of vasodilatation. Secondly, in each subject the systolic blood pressure, after an initial pronounced fall, returned to its resting level a little before, or shortly after, the onset of headache (Fig. 7). In neither subject did the facial flush fade

during the infusion. It seems probable that in these subjects some secondary reaction occurred, which successfully counteracted the depressant action of histamine on the arterial blood pressure, and that this was associated with the development of headache.

It is evident from these observations that the development of headache is associated with the recovery of the arterial blood pressure from its fall and, to a less extent, with the subsidence of raised cerebrospinal pressure. That the period of lowered blood pressure and of raised intracranial pressure is not merely preparatory, but is actually inhibitory, to the headache will now be shown.

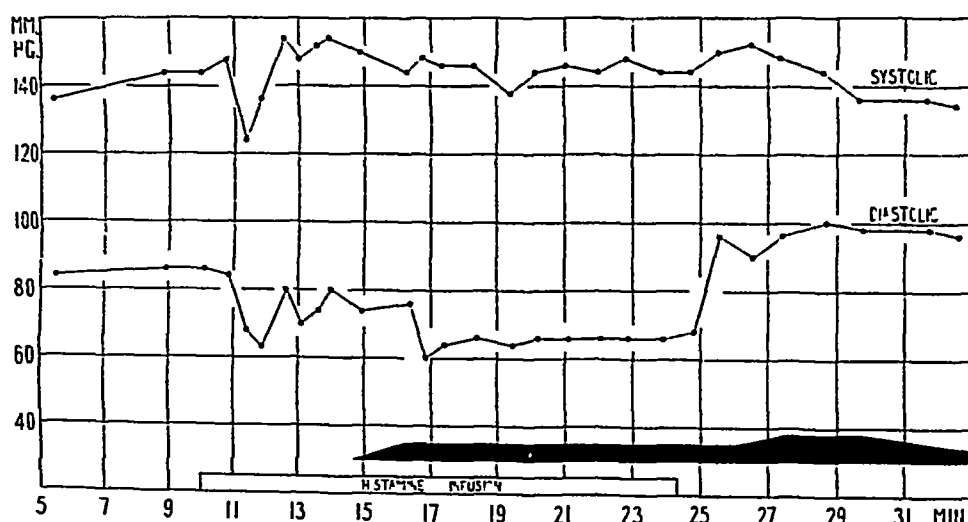


Fig 7 G Oct 13th, 1932 Shows the course of systolic and diastolic blood pressures and of the headache in response to an intravenous infusion of histamine at the rate of 0.11 mg per minute

The effect of a second injection of histamine

In 8 observations on 5 subjects, a second injection of histamine has been given when the headache due to a first was at its height. In each case, coincident with, or shortly following, the second flush, the headache disappeared completely, to return as the dilator effects of the second injection subsided. Thus headache disappeared, on an average, 4 seconds after the flush, remained absent for a further 22 seconds and then returned, gradually attaining or surpassing its original intensity. The disappearance of the headache was associated with the usual fall of blood pressure and rise of lumbar pressure. The following protocol shows a typical observation in which the blood pressure was recorded.

Protocol 1 Oct. 13th, 1932 Subject W. H., lying down for 10 min. before the observation began			
Time	B.P.	mm Hg	
Min. Sec.	syst.	diast.	
0 00	116	88	
0 30	116	88	
1 14	117	84	
2 15			Injection 0.1 c.c. 1:1,000 solution histamine acid phosphate intravenously
2 30	116		
2 35			Taste and flush
2 40	94		
3 00			Throbbing in the head
3 03	120		
3 05			Headache begins
3 10	130	94	
3 25	124		Headache getting worse
3 43	130		Headache severe
3 53			Injection 0.1 c.c. 1:1,000 histamine acid phosphate intravenously
3 55	128		
4 10	126		
4 23			Taste and flush headache gone
4 30	92		
4 47			Throbbing in head flush full
4 53	126		Headache begins again
5 05	126		Headache now much worse
5 22	126	90	Headache now very severe flush fading
5 30	128	94	
6 14	128	96	Headache now beginning to lessen
6 35	127		
6 55			Headache now moderate, throbs gone
7 25	124	94	
7 30			Headache now slight
7 52	122	94	
8 0			Headache nearly gone
8 20	120		

It has now been shown that a close relationship exists between the physical changes due to vasodilatation and the development of headache, the pain fails to appear, or is inhibited, when the physical changes are most intense, and begins as these subside. This finding strongly suggests that the headache is due to a mechanical disturbance arising out of, and residual to, the action of histamine on the vessels, it is entirely inconsistent with the view that the headache is due to a chemical change. For, if the pain were chemical in origin, then the latent period elapsing between the beginning of vasodilatation and the onset of headache would represent the time taken for histamine, or some product of its action, to attain an adequate concentration around the pain nerve endings. But it has been shown that the latent period may be lengthened by prolonging the injection, and that a pre-existing headache is abolished by a second injection of histamine for a period corresponding to the usual latent period. This abolition of headache is due, not to any specific chemical effect of histamine, but to vasodilatation, for a similar effect follows the inhalation of amyl nitrite, a substance producing profound vasodilatation in which the cerebral vessels share (26). While this dilatation is intense a histamine headache is abolished, as the following protocol shows.

Protocol 2 Aug 17th, 1932 Subject W H, lying horizontal on couch			
Time	B P	mm Hg	
Min Sec.	syst	diast	
0 00	117	80	
2 30	120	80	
3 00	116	78	
5 00	118	74	
6 30	118	78	
6 53			Injection 0.1 mg histamine acid phosphate intravenously
7 15			Taste and flush
7 25	102		
7 42	118	84	
7 45			Throbbing headache begins
8 10	128		Headache very severe
8 30	126		Flush nearly gone
8 53			Inhalation of 0.3 c.c. amyl nitrite
9 05			Headache less Face flushing
9 07			Headache gone
9 20	88		Inhalation stopped Flush full
9 30	112		Throbbing ache returning
9 55	118		
10 40	130	108	Severe throbbing headache
10 50			Flush practically gone
11 10	136	96	
11 50	122	90	Flush quite gone ache now moderate
12 30	128	90	Ache much less now
14 05	123	86	Very slight throbbing ache
17 00	122	78	Ache very slight, not throbbing
28 00	122	84	Ache gone

Comment on current theories Before presenting further evidence which indicates the nature of the disturbance producing the histamine headache, it will be well briefly to consider whether this pain can be accounted for on current theories

Because headache is the most prominent symptom of a number of pathological conditions in which intracranial pressure becomes raised, and because it is relieved by operation for relief of tension, the pain has been ascribed to stretching of the parietal dura mater by the pressure of the underlying structures. Histamine also raises the intracranial pressure, but it is already obvious that this is not the cause of the pain, for there is no synchronism between the rise and fall of intracranial pressure and the beginning and ending of headache.

A second theory, put forward by Trotter (23) to explain headaches of organic disease of the brain, and those following lumbar puncture, is that the pain arises from stretching of the intracranial septa. Since histamine will affect both hemispheres equally, a deflection of the falx can hardly occur in normal subjects. In patients presenting a large eccentric opening of the cranial vault (see Fig 3), a deflection of the falx to the side of the defect might be expected at the height of the histamine vasodilatation, in these, as in normal subjects headache fails to develop until vasodilatation is subsiding. Stretching of the tentorium would occur if a difference in pressure were established on the two sides of this membrane, for example, by impaction of the brain, at the isthmus. That this pressure difference does not occur is indicated by the similarity between the curves of lumbar

and intracranial pressure separately recorded (Figs 1 and 3). Further, the lumbar and intracranial pressures have been simultaneously recorded in a girl, aged 10, presenting a cranial defect, 6 cm in diameter, in the parietal region, through which a meningioma had been removed 7 months previously. In this patient, after intravenous injection of 0.07 mg histamine, both pressures rose, reached peaks and subsided to their initial values simultaneously. Headache developed as the pressures fell, and was severe when both were normal. Thus, in this observation, headache was present when the pressures both above and below the tentorium were the same as before the injection of histamine.

While the headache cannot be ascribed to one of the more obvious forms of stretching to which parts of the cranial contents are liable, yet there is strong evidence that the pain is due to tension. Thus it has been shown that the pain is greatly increased by rapid movements of the head which must strain the meninges. More conclusive are the observations, now to be described, which show that the pain may be lessened or abolished by a simple raising of cerebrospinal fluid pressure, or by a simple lowering of arterial blood pressure.

The effect on the headache of raising cerebrospinal fluid pressure

If the jugular veins are compressed in the neck, a histamine headache, produced in the usual way, is at once lessened, and remains so while the compression is maintained (30-60 sec). On releasing the compression headache immediately increases, attains for a moment an unusual severity, and then quickly returns to its customary level. The relief and return of headache are coincident with a rise and fall of cerebrospinal fluid pressure observed if lumbar puncture has been performed. Prolonged straining, as at stool, produces a similar or even greater degree of relief, the headache being also momentarily increased when straining is stopped. This act is accompanied by a transient and small rise of blood pressure (5-10 mm Hg), by considerable engorgement of the face, and by a large rise in cerebrospinal fluid pressure (20-30 cm H₂O). A smaller, yet definite, degree of relief is produced by lowering the head of a previously horizontal subject lying on a swing couch. A headache produced in the horizontal position is a little intensified by standing up*.

These observations do not make it clear whether the relief of headache is due to a rise of cerebrospinal fluid pressure or to a rise of intracranial venous pressure. That it is the rise of cerebrospinal fluid pressure which lessens headache is shown in the following way. We found, by chance, that a

* The effects of a rise of intracranial pressure are less striking when this is produced before the injection of histamine and maintained throughout the course of the succeeding headache. Thus, compression of the jugular veins, before the injection of histamine and maintained until headache disappears, does not appreciably influence the times of beginning and ending of headache, though lessening its intensity. A given dose of histamine produces similar headaches when the subject is in the horizontal, head down, or sitting positions.

prolonged histamine headache, previously relieved by jugular compression, was intensified by the same procedure after the withdrawal of 15 c.c. of cerebrospinal fluid. This result we have confirmed in a slightly different way in two patients, one of whom was the subject of Fig 8. In this patient headache, developing after the injection of 0.12 mg histamine, was relieved as usual by jugular compression. When this headache had disappeared 15 c.c. of cerebrospinal fluid were withdrawn, and 0.07 mg histamine injected intravenously. The resultant headache was twice found to be increased by the same degree of jugular compression as that previously used, while

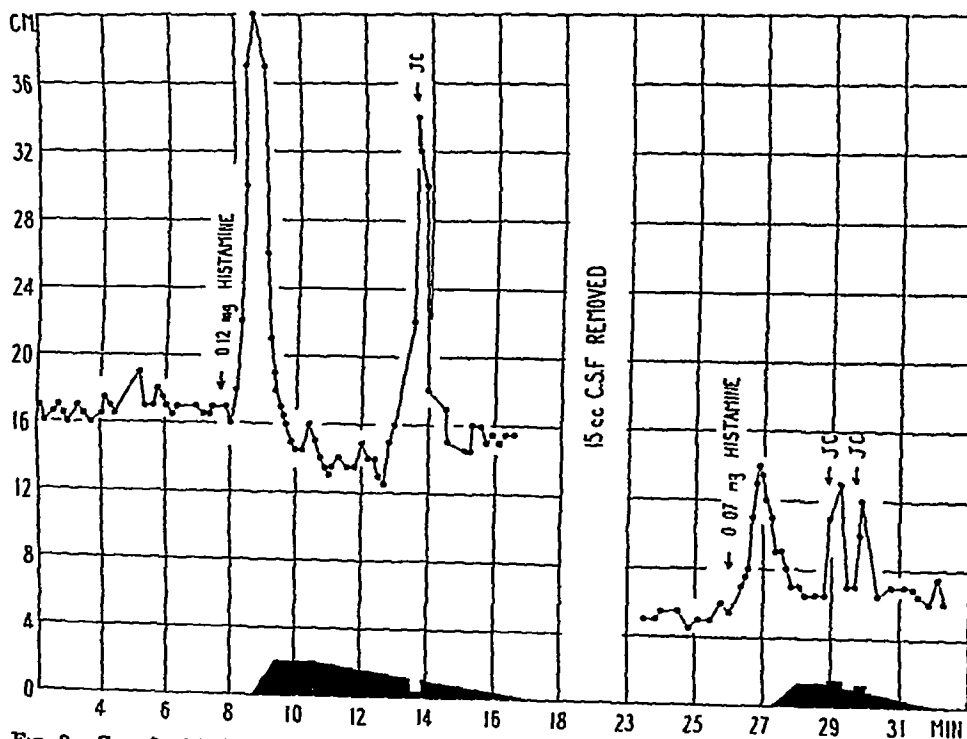


Fig 8 Case 3 of Table I Disseminated sclerosis, age 47 June 13th, 1932 To show the effect of jugular compression (JC) on the cerebrospinal fluid pressure and on the headache before and after withdrawing cerebrospinal fluid. After the first injection of 0.12 mg the pressure rose so much that about 0.5 c.c. ran out of the top of the 40 cm long manometer tube. The fall of the pressure below its resting level afterwards is thus explained. The second injection of histamine was reduced to 0.07 mg as the first headache was rather severe.

the associated rise of cerebrospinal fluid pressure was much reduced. This reduction may be ascribed to the inability of the intracranial venous channels to expand, since they are already distended to compensate for the volume of fluid withdrawn. Since the rise of intracranial venous pressure induced by jugular compression depends only on the degree of obstruction imposed, it

may be assumed to be the same before and after withdrawal of cerebrospinal fluid. This observation therefore suggests that a rise of intracranial venous pressure in itself tends to aggravate headache, ordinarily this effect is outweighed by the inhibiting action of the concomitant rise of cerebrospinal fluid pressure.

Direct evidence that a rise in cerebrospinal fluid pressure itself relieves the headache has been obtained from observations made on three patients, in whom 20 c.c. of warm normal saline were injected into the lumbar subarachnoid space. An observation on one patient is summarised in Protocol 3 and Fig. 9. The other two, suffering from peripheral neuritis and progressive muscular atrophy, behaved in essentially the same way, headache being quickly abolished by the injection of saline, but its recurrence with the fall of cerebrospinal fluid pressure was less striking than in the example given.

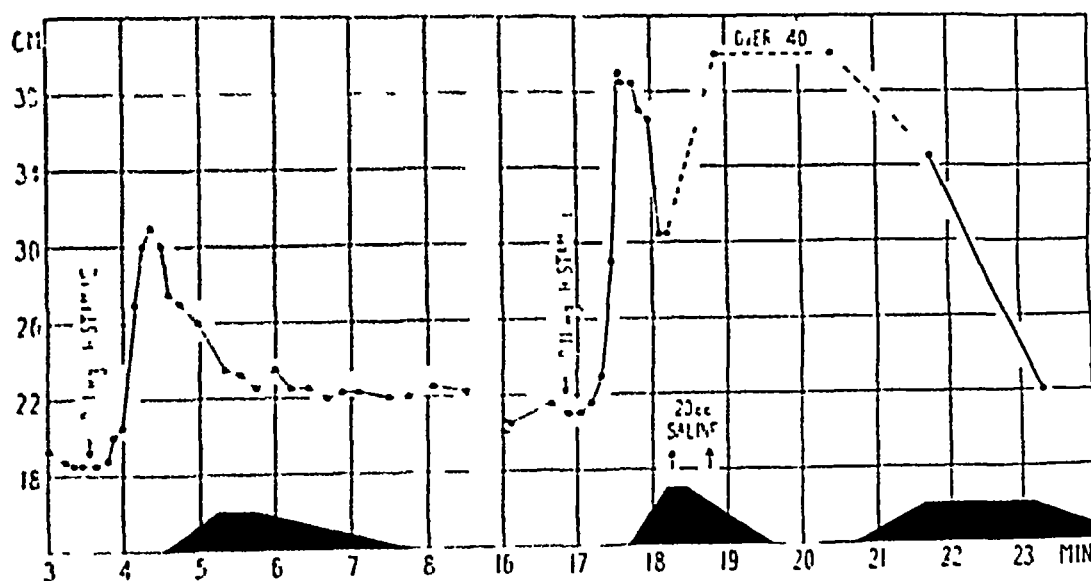


Fig. 9 illustrates Protocol 3

Protocol 3 February 17th 1973 G.A., male, aged 56, disseminated sclerosis. Lumbar puncture performed with patient lying on his side, the head raised about 6 cms above the level of the ascrum. After the removal of 4 c.c. of cerebrospinal fluid for diagnostic purposes readings of cerebrospinal fluid pressure were begun and are charted in Fig. 9. Respiratory and pulse oscillations were conspicuous. The times of the injections and of the statements made by the patient were as follows —

Min	Sec	Notes
1	45	Injection of 0.11 c.c. 1,000 histamine acid phosphate into forearm vein
1	52	Face flushes
4	32	Headache begins in parietal region
5	15	Ache at its height, moderately bad, throbbing
5	45	Ache getting less
6	33	Ache slight
7	16	Headache gone
16	50	Injection 0.11 c.c. 1,000 histamine acid phosphate intravenously
17	7	Face flushes

conspicuous directly after the onset, and steadily declines during the course of the headache, being unnoticeable during the later stages. Rarely the headache may be throbbing to the end. Occasionally, and particularly when the headache is slight, the pulse fails to affect it at any stage.

Muller's experiment In Muller's experiment the lungs are emptied to their full extent, the glottis closed and a forcible inspiration made. The result is a fall of 15-20 mm Hg of the arterial blood pressure, an effect due to stagnation of blood in the thorax, consequent on the strong negative pressure there set up. Crowden and Harris (5) have shown radiologically that, in this act, the volume of the heart is augmented and the density of the lung root shadows increased. When a histamine headache has developed, the performance of Muller's experiment lessens the intensity of the pain, which returns to its customary level when normal respiration is resumed. The relief is not due to a rise in venous pressure for we have never observed significant congestion of the face during the experiment, nor have we experienced any relief of pain by holding the breath for a similar length of time. The following protocol illustrates these observations.

Protocol 11 Subject W. H., August 22nd, 1932. Lying horizontal on couch

Time	B. P.	mm Hg.	
Min.	Sec.	Syst. diast.	
0 0		112 80	Injection 0.1 mg. histamine intravenously
0 10			Ta to and flush
0 35		94	
0 45		104	
0 55		110	
1 0			Throbbing ache begins
1 15			Ache more vivid
1 35			Muller's experiment begun
1 50		94	
1 55		92	Muller's experiment finished—subject says ache has disappeared
2 5		114	Ache back, throbbing worse than before
2 25		118	No change
2 55			Muller's experiment begun
3 08		94	
3 12			Muller's experiment finished, ache has gone
3 19		110	Ache has returned
3 28		112	
3 40		112	
4 15		112	Trace of ache only

Valsalva's experiment It has already been remarked that prolonged and gradual straining, as at stool, is associated with conspicuous congestion of the head and with relief of headache. If, however, the act is performed a little differently, and a sudden very forcible expiration made with the glottis closed, little congestion is produced, while the arterial pressure, for a few beats of the pulse, rises by more than 20 mm Hg. Performed in this way, Valsalva's experiment momentarily intensifies the pain.

From these observations we may conclude that a change in the arterial blood pressure produced in a simple mechanical way, without any active changes in the arteries, modifies the intensity of the headache: a rise accentuating and a fall lessening the pain. Changes in the arterial blood

pressure produced by acts, such as muscular exercise, in which the tone of the vessels is known to alter, have inconstant effects on the headache. In four subjects in the horizontal position we have investigated the effects of raising and lowering each leg alternately, exercise chosen to prevent movements of the head which are known to accentuate headache. In 3 subjects such exercise failed to affect the intensity of the pain, though blood pressure was raised 20 mm Hg. The fourth subject experienced aggravation of the headache during this exercise in numerous trials.

DISCUSSION

From evidence already given, we have been led to believe that the headache arises in the meninges and is caused by some simple mechanical disturbance which develops as the changes in blood pressure and cerebrospinal fluid pressure, produced by histamine, subside. This mechanical disturbance seems to be a tension effect which may be increased by certain acts and decreased by others, thus producing an increase or decrease of headache, respectively. While, at the moment, any final conclusion is unwarranted, some suggestions may be made as to the possible nature of this tension phenomenon.

The relief of headache when the cerebrospinal fluid pressure is raised, or the arterial pressure lowered, suggests that a factor determining the intensity of headache is the diameter of the intracranial arteries, for the pain is lessened by a rise of pressure outside these vessels* or by a fall within them. For this reason we suggest, as a tentative hypothesis, that the pain arises from a stretching of some sensitive structure lying either in the arterial wall or in the surrounding perivascular tissues. On the view, previously expressed, that the headache originates from the dura mater, the vessels concerned would be the meningeal arteries, it has already been seen that the tissue around these vessels seems to be sensitive to direct stimulation. As it is unlikely that shaking the head can strain the vessel walls themselves, it seems not improbable that the headache actually originates from the perivascular tissues. The question remains as to how histamine may set up a state of tension in these perivascular structures.

As one possibility, it may be suggested that when headache is present the arteries are normal in size, and that tension is due to oedema of the perivascular tissues, such oedema might be conceived to result from the increased vascular permeability that histamine is known to produce (18), and clearly might persist when the vasodilator effects of histamine had subsided. A second possibility is that tension is set up by a widening of the meningeal arteries due to the action of histamine on their walls. This view,

* Wolff and Forbes (27) observed in cats under amytal anaesthesia a widening of the pial arteries when cerebrospinal fluid pressure was greatly raised (40—110 cm. of water), an effect attributed to asphyxia. With increments of pressure comparable with those here employed it is evident from their Figs 2 and 8 that the pial arteries narrowed slightly.

however, could only be reconciled with the persistence of headache after the evident vascular changes have subsided, by assuming that the dilator action of histamine on the intracranial arteries outlasts its action on the minute vessels*. During the first stage in the response to histamine, expansion of the intracranial arteries would be hindered by the rise of pressure outside these vessels and the fall within them. As the minute vessels narrowed, and the arterial pressure rose, so the arteries would be free to expand and their expansion would last so long as histamine relaxed them.

To recapitulate, our observations would be completely explained if headache were due to stretching of a sensitive structure lying close to the meningeal arteries, such stretching might result from swelling of the perivascular tissues or from widening of the meningeal arteries.

Since the mechanism of headache is a subject still relatively unexplored, two alternative explanations and the reasons for their rejection will be considered.

To account for the delayed onset of headache we suggested in a preliminary communication (21) that an expansion of the brain might redistribute cerebrospinal fluid in a manner not immediately reversible on the subsidence of vasodilatation and that this change might set up a state of tension in the vascular meninges, and so produce headache. This explanation we now find to be untenable since it is incompatible with our more recent observations that the injection of 0.1 mg. histamine and the inhalation of 0.3 c.c. amyl nitrite mix, in the same subject, and on the same day, produce an identical expansion of the brain as judged by the rise in lumbar pressure, while only histamine is followed by headache. 0.3 c.c. amyl nitrite may also lower blood pressure as greatly as does 0.1 mg. histamine, yet, although it is said sometimes to produce headache, it has failed to do so in all of 6 subjects, examined by us, who were susceptible to histamine. Why histamine should be more potent than amyl nitrite in producing headache is uncertain. It is known, however, that histamine increases the permeability of the minute vessels (17), which amyl nitrite has not been shown to do. An increase in vascular permeability might be a factor in producing headache if the pain were due to the mechanism first suggested or to the following.

A second possibility is that the headache may result from ventricular distension with inequality of the cerebrospinal fluid pressures within and without the ventricles, such a condition might result from an increased formation of cerebrospinal fluid due to the action of histamine on vessels

* This hypothesis has not been tested in man, for this implies direct observation of the intracranial arteries with the cranial cavity closed. The observations of Forbes, Wolff and Cobb (10) are not directly relevant, since they were made on anaesthetised cats, and the vessels observed were smaller than those we have in mind.

of the choroid plexus * This hypothesis was suggested in a reply to our preliminary communication by O'Malley (19) who considered the rise of cerebrospinal fluid pressure to signify an increased secretion, an interpretation which cannot be accepted, since the rise can be accounted for by the cerebral vasodilatation that is known to occur It is possible, however, that increased secretion, leading to ventricular distension, might occur without being evident from the curve of cerebrospinal fluid pressure For an increased formation of fluid within the ventricles might be balanced by an increased absorption from the subarachnoid space, favoured by the rise in cerebrospinal fluid pressure due to vasodilatation The hypothesis that the pain results from ventricular distension is not incompatible with the relationship between the development of headache and the changes in cerebrospinal fluid and arterial pressures following the injection of histamine For the rate of formation of fluid depends not only on the permeability of the capillaries, but also on the pressure difference inside and outside these vessels The formation of fluid would thus be inhibited by raised intracranial and lowered arterial pressure, and would occur at an increased rate only as these returned to normal Again, a simple rise of subarachnoid cerebrospinal fluid pressure might abolish the pressure difference within and without the ventricles and so relieve headache The establishment of a difference in pressure within and without the ventricles would have to depend on obstruction to the outflow of fluid into the subarachnoid space This is usually considered to be possible in the Aqueduct of Sylvius, but it is still uncertain if this canal is ever sufficiently narrow in the normal living brain appreciably to hinder movements of fluid A serious objection to the hypothesis of ventricular distension is that it fails to explain why the intensity of the pain can be modified by simple alterations in the arterial blood pressure Moreover pain arising from ventricular distension would result, presumably, from stretching of the velum interpositum of the third ventricle, a structure which, according to Stöhr (21), is innervated by cranial nerves other than the fifth Cushing's (4) recent comparison of intramuscular and intraventricular injections of histamine is not directly relevant, headache being only briefly mentioned, and though it would seem that intraventricular injection is more potent in producing headache, this is explicable by any theory that attributes headache to the action of histamine on an intracranial structure

The observations here described have shown that one variety of headache has well defined characteristics and have suggested an explanation of its mechanism Their interest would be heightened if the relationship were known between the headaches occurring naturally in disease and that produced by histamine This is a problem for future investigation and cannot

* Dixon and Halliburton (7) found that histamine produced a sucking back followed by an increased flow of cerebrospinal fluid from a cannula in the cisterna magna, the later effect being attributed to asphyxia Their method has been adversely criticised by Weed and Cushing (24) and by Becht (1) and their results obtained on dogs under urethane and morphia anaesthesia are not applicable to anaesthetised men

be dealt with fully here. We have noticed, however, that several workers in this laboratory are subject to mild headaches of the type common in normal people, and of unascertained cause. These headaches are usually frontal, may be throbbing, are aggravated by shaking the head, relieved by jugular compression and temporarily abolished by the injection of histamine. In brief, their mechanism would seem to be identical with that of the histamine headache. The post lumbar puncture headache is typically a throbbing frontal ache aggravated by shaking the head, and by jugular compression. This type thus differs from the histamine headache only in the customary relief of the latter by jugular compression. This apparent difference is actually a point of resemblance for the post lumbar puncture headache is said to be associated with a low cerebrospinal fluid pressure (12), and the histamine headache is aggravated by jugular compression after the withdrawal of cerebrospinal fluid. It may be suggested, therefore, that the disturbance producing the post lumbar puncture headache is similar to that evoked by histamine, but this again needs further investigation.

CONCLUSIONS

1. Headache is easily produced in normal subjects by injecting 0.1 mg. histamine acid phosphate intravenously. This headache has certain well defined characteristics.

2. The headache is shown to arise from an intracranial structure, probably meningeal, and innervated by the trigeminal nerve. Anatomical evidence suggests that this is the dura mater.

3. Histamine produces a rise of cerebrospinal fluid pressure, due to cerebral vasodilatation, and a fall of blood pressure; headache develops as these pressure changes subside. This relationship suggests that headache is due to a mechanical disturbance resulting from and residual to, the action of histamine on the vessels.

4. Because headache is relieved by raising the cerebrospinal fluid pressure or by quickly lowering the arterial blood pressure, it is suggested, as a tentative hypothesis, that the pain may be due to stretching of a sensitive structure lying close to the meningeal arteries. Such stretching might conceivably arise from swelling of the perivascular tissues, or from widening of the arteries.

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OBSERVATIONS ON ANGINA OF EFFORT *

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It is natural that attention should have been attracted repeatedly to so important a syndrome as that of angina pectoris. Whilst there are many accounts of subjective sensations, few records have been made of changes taking place in the cardiovascular system during attacks. Yet objective studies are most desirable, if we are to increase our knowledge of the condition. The attacks, to which interest has largely been directed in the past are severe and prolonged, and take place, as a rule, in circumstances which render precise and instrumental observation difficult. Lewis (17) has recently defined a particular type of anginal syndrome, and has reported a series of cases in which, during attacks, pulse and blood pressure readings were obtained. This type occurs usually, but not exclusively, in cases of free aortic regurgitation, and the attacks of pain, which are not constantly related to any single causative factor, are associated with high pulse rate and blood pressure. Another syndrome, that which arises when one of the larger coronary vessels is suddenly occluded, has been recognised, and this has explained many obscure cases in the older descriptions of angina pectoris.

It is, however, for less severe pain, arising behind the sternum after exercise, that the majority of angina patients first seek medical advice. It was to this "disorder of the breast" that Heberden (12) first gave the name "angina pectoris," because it produced a "sensation of strangling" in some patients. "Those who are afflicted," he writes, "are seized whilst they are walking with a painful and most disagreeable sensation in the breast, the moment they stand still, all this uneasiness vanishes." In the short and remarkably accurate account which follows, he describes this type of angina pectoris, the angina of effort. In those who suffer in this way, attacks can be induced at will, and the relationship of the pain to changes in the cardiovascular system can be determined. We have chosen this type of angina for study, and limit the term in this paper to those cases in which pain of anginal type is produced by physical exercise, and by no other means. We can find only two accounts of angina of effort based on personal

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observation of the attacks (Bischoff (3), Wood and Wolferth (31)), and these do not contain adequate information about the relationship of the pulse and blood pressure to the onset of pain. Bischoff (3) describes some of the features of induced attacks, but he gives no details of his patients, and makes only general statements about the alterations in blood pressure. Wood and Wolferth (31) examined a number of cases to see if they could detect electrocardiographic changes during attacks of angina, and incidentally recorded variations in blood pressure. Some of these attacks were induced by exercise, and the history and short duration of the pain suggest that several of the cases were of similar type to those in the series we are about to describe. Observers have naturally been averse to provoking attacks of angina deliberately, fearing to establish severe seizures. But in dealing with angina of effort and setting a patient to do exercise, he is asked to do no more, while under close control than he is in the habit of doing several times a day, without supervision, when he walks until pain arises. To institute such tests is clearly justified by the considerable information it gives about each patient.

When we came to examine a number of cases of angina of effort, it was found that, in several, the amount of exercise required to produce pain in any one individual under standard conditions was surprisingly constant. Advantage was taken of this fact to vary experimentally the circumstances in which the pain was induced, noting the effects of such variation upon the pain and its duration.

Method

We have made our observations over a period of a year on eleven patients, in whom effort, and effort alone, induced attacks of anginal pain. It was thought more advisable to investigate exhaustively a small number of carefully selected cases, eliminating chance errors by repeating all observations, than to study a larger group of patients which might have included cases of unusual type, or given results differing in detail from those obtained.

Our subjects were all males, and their ages ranged from 47 to 68 years. Three gave a history suggestive of previous coronary thrombosis, and in one of these the fact was confirmed after death. Two were cases of aortic regurgitation, one of syphilitic, and one of doubtful etiology but probably due to annular sclerosis. The remaining six had symptoms of slow onset, and showed in addition to anginal pain on exertion, evidence in greater or less degree of myocardial impairment. A summary of the main clinical features of the cases is given in the appendix at the end of the paper.

Observations were made as a rule on each case at a fixed time of day. The patient was requested to take his meal two to three hours before arriving at hospital, to travel by foot as little as possible, and to take no medicine on that day. He was allowed to rest in a chair in a comfortably warm room for at least a quarter of an hour or longer, until the pulse and blood pressure had reached a steady level. He was then asked to walk up two steps to a

platform, down two steps on the other side, to turn round and come back again. The height of the lower step was 9 inches and of the upper 6 inches. This exercise was repeated at a steady rate until the patient said that pain was present, when he was asked to sit down, and the number of times he had climbed to the platform was recorded as the "number of efforts". Pulse and respiratory rates and blood pressure readings were then resumed, and taken as frequently as possible until steady levels were again recorded, and the time at which the pain passed off was noted. After fifteen minutes rest the test was repeated. In all the patients here used, an almost similar number of efforts gave rise to pain in two successive tests. Thus in Case 6, for example, 48 efforts were required to produce pain in the first test, and 58 when it was repeated 15 minutes later. In a further two repetitions, after similar intervals of rest, pain arose after 48 and 50 efforts respectively. The duration of the pain in these four consecutive tests was 1 min 37 sec, 1 min 30 sec, 1 min 30 sec, and 1 min 35 sec, respectively. In this way we obtained control observations which enabled us to detect the effects of varying the conditions under which the tests were made. As a rule, two control observations in good agreement were considered sufficient, but sometimes three were made, and in special circumstances one only was carried out. Each patient was allowed to choose his own rate of walking over the steps on any one occasion, but was kept to this rate, once it was chosen and found suitable, the slowest rate was 9, and the most rapid 13, efforts a minute.

All our cases were males of the hospital class, and there was no reason to suppose that suggestion tended to keep this onset of the pain constant. As a precaution, each patient was given from time to time, prior to one of the control tests, a drink of water or normal saline with the suggestion, actual or implied, that it would improve his performance or diminish the pain. Cases responding to these suggestions were excluded from the series.

The number of efforts performed in the control tests varied on different days in the same case, and such variations were used to measure the patient's progress. Apart from this, our conclusions are based on tests each completed and controlled at the same examination. The type of exercise chosen is particularly suitable, because the patient is always accustomed to it. It permits little or no information to be obtained about the pulse and respiratory rates and the blood pressure during the period of exercise. Four of the cases were submitted to exercise on the bicycle ergometer to obtain this and other information to be recorded, otherwise, the results obtained by this unusual exercise and by the standard method pointed to the same general conclusions.

Reactions to exercise

We have observed, and have full records of, over four hundred attacks of angina induced by effort. Though the amount of exercise required to produce pain differed considerably in different cases, the attacks themselves had so many points of similarity that general statements can be made.

The pain Patients described the pain while it was actually present, in this way, a much more accurate account is obtained than from attempts to remember the sensation of past attacks. The pain was nearly always retrosternal. One patient (Case 11) said that it usually started in the left shoulder blade, and then passed round to the front of the chest. Its onset was heralded in several cases by premontary feelings of tightness in the chest and vague retrosternal discomfort, but every patient developed characteristic pain easily identified with that for which he was seeking medical advice. The pain has a curious quality which patients find difficult to describe, "burning" and "gripping" are adjectives commonly used. In all the cases it was stated to be continuous and never throbbing. Its duration in most patients was sufficiently constant in control observations to enable the influence of various factors to be studied. In different individuals its average duration varied from 15 seconds to two and a half minutes. In general, patients were not allowed to continue exercise once pain had come, otherwise, the pain became worse and began to spread around the chest. We came to the conclusion that the more severe and lasting attacks which several patients described as having been experienced were brought about in this way.

Except in certain special observations under conditions tending to intensify the pain it was easily bearable and none of the subjects objected to repeating the tests. In no instance was it accompanied by anxiety, salivation and facial pallor did not occur, flushing of the face and sweating were noted in several cases, but were no greater than after a slightly smaller amount of exercise insufficient to cause pain.

Changes in pulse and blood pressure during the attack With the exception of Case 7 none of our patients had a resting systolic blood pressure greater than 150 mm Hg. Resting diastolic pressures were all below 100 mm Hg. After exercise sufficient to produce pain, the systolic blood pressure was raised above the resting level to a varying degree in the different cases. The diastolic blood pressure altered to a much smaller extent, usually rising or falling about 5 to 10 mm Hg*. In Case 3 the rise was very small, and in several observations the blood pressure was unaltered (Fig 1). The extent of the rise in all the other cases was much greater than in normal young adults after a similar number of efforts at similar rates. In some cases an actual rise of blood pressure was observed after the end of exercise, as described by Cotton, Rapport and Lewis (5) in normal subjects. Case 6 showed an unusually prolonged rise of this kind, the rise continuing for some time after the pain had passed off (Fig 2). In none of the cases studied could a particular threshold of blood pressure be distinguished at which pain might be expected. Often on the same day, in different control

* Unless otherwise stated, the term "blood pressure" will mean systolic blood pressure. On account of the small changes in diastolic pressure, the mean and systolic blood pressures will move in the same direction.

observations, pain appeared at very different blood pressure levels. It was thought possible that some part of the rise in blood pressure might be due to the presence of pain. To decide whether this were true or not, ten of the

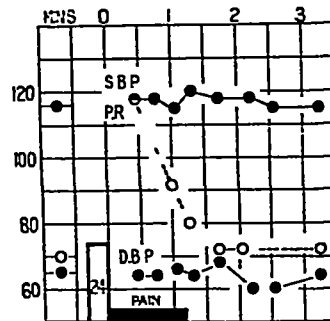


Fig 1 14 12 31 Case 3 Although pain occurs after exercise, the blood pressure is not raised. In this and subsequent figures —

S B P = systolic blood pressure in mm of mercury

D.B P = diastolic blood pressure in mm of mercury

P.R = pulse rate in beats per minute

On the left of the vertical rectangle are the resting readings before exercise was begun, to the right are the readings after the patient has sat down. The number included in the vertical rectangle and its height represent the number of efforts. The length of the black horizontal rectangle gives the duration of pain.

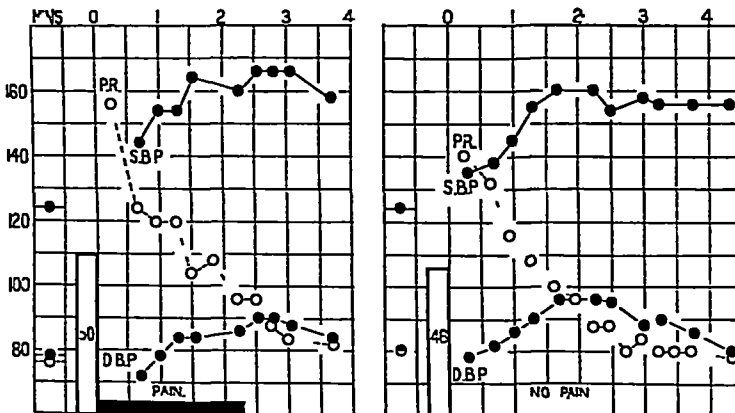


Fig 2 10.2 31 Case 6 The left chart shows a control test with the rise of blood pressure continuing after the pain had gone, the right chart records the results of a test in which the patient stopped a few efforts before pain was anticipated. The blood pressure readings are similar, but the pulse rate is lower than in the test in which pain occurred.

cases were tested by asking them to sit down shortly before they had completed the series of efforts previously found adequate to determine the onset of pain, but before it was actually present. The blood pressure often rose

quite as much in these experiments as in those in which pain was produced (Fig. 2), and occasionally it rose higher. The rise in blood pressure is due, therefore, to the exercise and not to the pain. One case (Case 4) presented a very unstable blood pressure, which during an exciting conversation, while the patient was resting and comfortable, would rise above the levels found during the attacks of pain after exercise. A similar result was obtained in Case 11 by distending the stomach with air. Thus we see that there may be no rise in blood pressure yet pain may come (Fig. 1), and that the blood pressure ordinarily associated with pain may be surpassed without pain appearing. It will be shown later, in our observations on the nitrites, that, in nearly every one of these cases, pain may occur while the blood pressure is no higher than its ordinary resting level.

The view that anginal pain results from the dilatation of a diseased aorta put forward by Allbutt (1), and adopted by Wenckebach (29), though losing ground, is still widely accepted. The case against it has been ably summarised by Keefer and Resnik (15). If the hypothesis is true, the attacks of pain should be related strictly to the height of the blood pressure, since this alone can increase the tension of the aortic walls. Lewis (17) found that this was not so in the anginal syndrome he described. We find that similarly it fails to hold in angina of effort.

Pulse rate. In Case 7 the resting pulse rate was consistently above 100, exercise sufficient to produce pain raised the rate to 150. The other patients had pulse rates within normal limits at rest and after exercise sufficient to induce pain, the rates lay generally between 110 and 130 and usually around 120. Unlike the blood pressure, the pulse rate soon fell with rest, rapidly during the first minute, and then more slowly to reach the resting level after times varying considerably in different individuals, but, in the majority of cases, the pain passed off when a definite pulse rate had been reached, some 10 to 20 points above the resting level. This remained true irrespective of the behaviour of the blood pressure which, as already mentioned, often continued at a high level. When exercise was stopped just before the expected onset of pain, it was unusual, and if the blood pressure was equally raised, quite exceptional, to find the pulse rate as high as in a test in which pain was induced. It is, of course, possible that pain may itself be responsible in part for this additional increase in pulse rate, but the equal rapidity with which the pulse rate fell, whether pain was present or not, suggests that this is not the case.

These pulse and blood pressure observations, with their relationship to the appearance and disappearance of the pain, must guide us in determining what is happening in the heart. We have shown that the alterations in blood pressure are, in themselves, inadequate to explain the onset and disappearance of pain, and that, on the other hand, a much closer relationship to the rise and fall of the pulse rate exists. According to the recent work of Rein (21) and Hochheim (11), the coronary flow in the normal heart is

nicely adapted to the work which it is called upon to perform. As pointed out by Lewis (18), it is the internal work or energy expenditure of the heart which is relevant to the problem, rather than its external work as indicated by the output and blood pressure. An increase in the rate of the heart will increase this expenditure, since the pressure in the ventricle must be raised at each beat from intraventricular diastolic to diastolic arterial pressure before any external work is done. Using the heart-lung preparation, Starling and Visscher (25) showed that the heart uses less oxygen to do a given amount of work when the rate is slow than when it is rapid. Increasing the heart rate thus decreases its efficiency. In attacks of paroxysmal tachycardia, and in paroxysmal fibrillation and flutter, it is well recognised that angina pectoris may occur (Mackenzie (19), White and Camp (30)). Here the mean blood pressure and the output of the heart are both reduced, and hence its external work is diminished. Its energy expenditure, on the other hand, is greatly increased, and although the coronary flow is not affected, as judged by the effect of similar heart rates in animal experiments, the discrepancy between the two may be so great as to give rise to anginal pain. The attacks of angina which sometimes occur in hyperthyroidism (Lev and Hamburger (16)) are, no doubt, due in part to the tachycardia which is usual in this condition.

When exercise is taken, the rise in blood pressure and in heart rate increase the energy expenditure of the heart, but the change in the heart rate is the more important of the two. In the heart with diseased coronary vessels, the normal adaptation of increased coronary flow to increased energy expenditure fails, and a relative myocardial ischaemia results. The mechanism by which this gives rise to pain has already been discussed by Lewis (18), and our results are wholly in agreement with his views.

Dyspnoea Three of our patients (Cases 3, 8 and 9) showed no greater increase in respiratory rate and depth than was produced by the same amount of exercise in a normal subject. Even when pain was present, these patients had no respiratory embarrassment. They also showed consistently lower pulse rates after exercise than did the others. These others became more breathless than normal individuals after a similar amount of exercise, and were always definitely breathless after exercise sufficient to produce pain. When the exercise was stopped just before the onset of pain, however, they showed respiratory rates equally high. It appears, therefore, that there is no direct association between pain and dyspnoea in this type of angina pectoris. It is possible that those individuals who have no respiratory distress when pain arises possess a relatively intact myocardium, and that, as suggested by Cowan (6), the pain arises from a small area to which the blood supply is inadequate for the work which it is called upon to perform. We are not, however, at the present, in possession of evidence which would serve either to confirm or to refute this suggestion.

Arrhythmia A few cases exhibited occasional extrasystoles at rest, in four (Cases 3, 6, 8 and 11) they were present when the pulse rate was

approaching its normal level after exercise, and often before the pain had passed off. Goldhammer and Scherf (11) who recorded ventricular extrasystoles electrocardiographically during attacks of angina, regard them as evidence of myocardial damage from a relative ischaemia. Just before, or just after the pain passed off four cases (Cases 3, 4, 6 and 7) exhibited alternation of the pulse, as judged by a difference in systolic pressure of 10 mm. or more between alternate beats. It is noteworthy that two of the three patients who died during the year of observation showed this phenomenon.

The effect of further exercise immediately after an attack. Details of an interesting case of angina of effort are given in a letter to Heberden (13) from an unknown patient who found that if he continued to walk during an attack, the pain gradually passed off in from 5 to 10 minutes. We have not yet met a patient with a similar history suitable for observation, and all our cases declared that the pain became more severe and tended to spread, if they continued their exercise. Observations on a few patients confirmed this statement. Several, however, said that if they started to walk again as soon as the pain had disappeared, they were able to travel a distance almost as great, or greater, than that which had originally given rise to an attack. Five such patients were studied to determine the effect of further exercise immediately after the disappearance of pain. When they were compelled to maintain the standard rate two performed a quarter, one a half, one three quarters and one the whole number of efforts which had given rise to pain in the first test. They showed, however, a tendency to a diminished rate in the second series of efforts, and, if this was allowed, more exercise was performed. Their impression was no doubt, due to such an unconscious slackening of pace. This observation emphasised the importance of checking such statements by objective tests whenever possible. In these observations at the time when the first attack of pain passed off, the blood pressure was always considerably raised, whereas the pulse had fallen to about 10 or 20 points above its resting level. When the second attack began, the blood pressure was often higher than in the first, but the pulse was always at the same level. These facts serve to confirm our view that the heart rate is the chief factor in determining the onset of the attack.

To test further the idea that the rate of the heart is the important factor in determining the onset and disappearance of pain, we examined the effect of atropine, and of pressure on the carotid sinus, on several of our cases.

The effect of atropine on the exercise and on the pain

Four of the less severe cases were chosen for this purpose (Cases 6, 8, 10 and 11). After two control tests in each, an intravenous injection of 1.3 mg. (1/50 grain) atropine sulphate was given, and five to ten minutes later, its effect being at its height, exercise was again undertaken by the patient until pain started. After a further 15 minutes rest, and with a full atropine effect on the rate of the heart still present, a second observation was

made In one of the patients, in whom such comparisons were made (Case S), the number of efforts was halved, and the pain lasted ten times as long as in the control observations This occurred in spite of a reduced level of blood pressure (Fig 3) The three other cases gave similar and quite

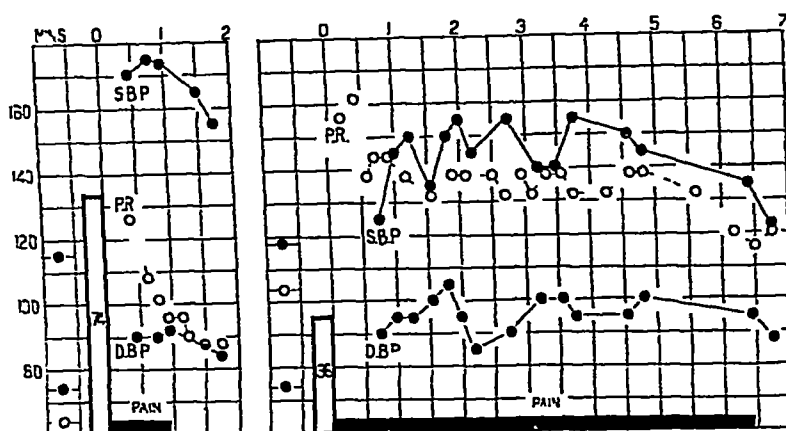


Fig 3 6 6 32 Case S The chart on the left shows a control test, that on the right the effect of exercise after 1.3 mg ($\frac{1}{4}$ grain) of atropine sulphate had been given intravenously. The number of efforts is diminished, and the duration of the pain greatly increased. The general level of the blood pressure is lower and of the pulse rate much higher than in the control test.

definite, though less pronounced results of the same type. This action of atropine is important for several reasons. In animals it gives a decided increase in the bloodflow through normal coronary vessels. According to Rein (21), it does so by releasing the tonic action of the vagus, which, as Anrep and Segall (2) first showed, is the vasoconstrictor nerve to these vessels. To explain our results, it might be suggested that atropine is unable to dilate the diseased coronary system in man, but the four cases in which atropine had an adverse effect, showed a definite increase in exercise tolerance after nitroglycerine, thus showing that the coronary vessels were capable of dilating, at least to direct chemical influences. If it were merely failure to improve after atropine, it might be suggested that this drug acts, in the normal animal, only upon the larger branches of the coronary arteries, which in our cases were so diseased that they could not be affected, whilst the nitrites act on smaller vessels still capable of some response. But we have, in fact, to explain the diminution in the number of efforts and the increase in the duration of the pain under atropine, and can attribute this only to the more rapid action of the heart, which increases its energy expenditure without a concomitant increase in the coronary flow.

These observations also throw light on the theory, still widely held, that angina pectoris is due to a spasm of healthy or diseased coronary vessels.

This may quite probably be true of spontaneous attacks. It is an unnecessary assumption in the case of angina of effort and the constancy of the amount of exercise necessary to produce pain in any one patient renders it improbable. It is made even more unlikely since atropine hastens the onset of pain. In this connection some observations by Peller (20) are of interest. During attacks of spontaneous angina with considerable rise of the pulse rate subcutaneous injections of 10 mg (1/64 grain) of atropine were found to cause the pain to disappear. At the same time the pulse rate was considerably lowered, as would be expected after a dose of atropine, which, when given subcutaneously, often increases vagal tone. The diminution in the energy expenditure of the heart, brought about by this reduction in its rate, well explains the relief of pain and makes Peller's assumption of a dilatation of the coronary vessels unnecessary.

Allbutt (1) gave atropine systematically to all anginal cases in increasing doses in order to protect the heart against "inhibitive shock." This procedure is inadvisable until we are surer of the type of case in which a beneficial effect can be anticipated.

The effect of carotid sinus pressure on the pain

Firm pressure over the carotid sheath in the neck at the level of the bifurcation of the common carotid stimulates the carotid sinus, slowing the heart rate and producing a fall in blood pressure. Stella (26) has shown, using the heart-lung preparation that, in the dog, an increase in the pressure in the carotid sinus causes a diminished coronary flow. This is a vagal effect and occurs even if the heart rate is artificially maintained, so that there is no diminution in the minute volume of the heart, or in the blood pressure. Constriction of the coronary vessels, excited by a similar reflex in man, would tend to increase the duration of anginal pain. On the other hand the rapid fall in the heart rate and blood pressure, by diminishing the energy expenditure of the heart, should tend to exercise the opposite effect. In combination, these opposing effects might conceivably neutralise one another, but more probably one would predominate. The experiment is, in fact the converse of that in which the administration of atropine was studied, and the same considerations apply.

Nine patients were investigated. Control tests alternated with those in which firm pressure was exerted on the right sinus, as soon as the patient sat down with pain present. In some of the former, to eliminate effects which might have arisen from suggestion, pressure was made on the nape of the neck. The duration of the pain was decreased in all these patients by pressure on the carotid sinus. All showed a more rapid fall of blood pressure and pulse rate than in the control tests. In most patients, this lowering was more noticeable in the pulse rate, in some, the blood pressure was considerably, and in others only slightly, reduced. A typical chart is given as an example of the effect obtained (Fig. 4).

The effect of carotid sinus pressure on anginal pain has been recorded by two observers. Danielopolu (7) has reported a case of spontaneous angina, with raised pulse and blood pressure in the attack, in which pressure on the sinus relieved the pain. Wassermann (28) describes six cases in which attacks were relieved by carotid sinus pressure. The majority of these attacks were spontaneous, but five attacks induced by exercise are described, with blood pressure readings and pulse rates. His observations differ from ours, since the cases were not examples of pure effort angina in the sense in which we have defined it, and the length of time the pain would

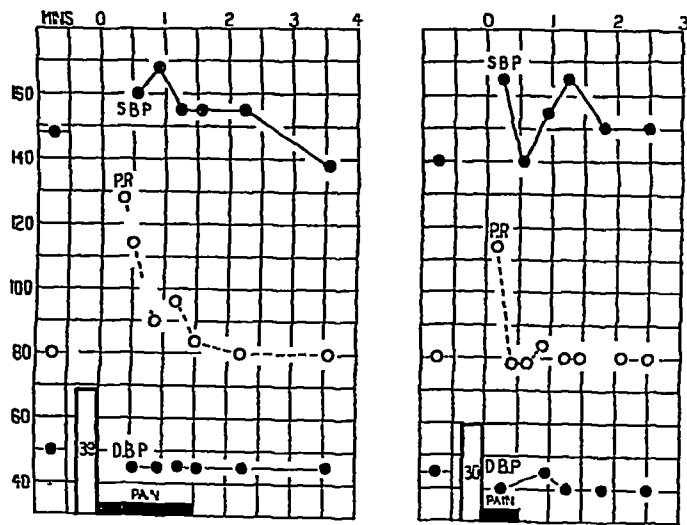


Fig 4 20 9 32 Case 4. The chart on the left shows a control test, and that on the right, the effect of pressure on the carotid sinus as long as pain was present. The pain stops shortly after the pulse rate has fallen abruptly to its resting level. The blood pressure also falls, but rises again when the pressure is released.

have lasted without interference was not ascertained by suitable control tests. The suggestions offered by these writers to explain this effect on the basis of special reflexes seem less likely to be true than our view, that relief is due to a diminished energy expenditure of the heart, caused primarily by a diminished heart rate, with or without a diminished blood pressure. This diminution in the energy expended more than outweighs any effect which pressure on the sinus may have in constricting the diseased vessels in man.

Evidence confirming our views has been obtained, and several fresh points of interest have been raised by studying the action of nitrites on the relationship of exercise and pain.

The action of nitrites on the onset and duration of pain

Although the relief of pain in angina by nitrites is universally acknowledged, and the knowledge widely applied, few precise records of their effect on the pulse and blood pressure are available. In the case of spontaneous attacks, Lewis (17) has collected a series of observations, adding and discussing several of his own. These, however, are not directly relevant to angina of effort. Burgess (1) examined the effect of the rapidly acting nitrites on the pain in a series of eight cases, said to be of "ambulatory" type. It is not stated that the attacks were induced by exercise, and the figures suggest that they were not.

In our series, we have investigated the effects of nitroglycerine and erythrol tetranitrate on the amount of exercise necessary to produce pain, and of these drugs and of amyl nitrite on the duration of the pain. The results of all the tests, nearly a hundred in number, were compared with control tests performed on the same day, and complete pulse and blood pressure readings are available for comparison. The results will first be recorded, and their significance subsequently discussed. In one case only (Case 1), was a response exhibited differing sufficiently from the others to require separate consideration.

Amyl nitrite. In all but one case out of 11, inhalation of amyl nitrite, within a few seconds of pain arising, reduced the duration of the pain. Doses of 0.18 to 0.30 c.c. (3 to 5 minims), such as we used, gave rise, when given immediately after exercise, to a considerable fall in blood pressure, and to a rise in pulse rate of variable extent. There was, however, no constant relationship between the time and extent of the fall in blood pressure and the disappearance of the pain, although the pain usually passed off in a half to one minute, or about the time of the maximum fall in blood pressure. After exercise, the fall in pressure when amyl nitrite was given was followed by an equally rapid rise, and sometimes the blood pressure had regained a high level before the pain passed off (Fig. 5 shows this effect). Again, in other cases, after the pain had disappeared, the blood pressure rose to a higher level than was found in control observations with pain present. Our results, which will be discussed later, suggest that the relief of pain after amyl nitrite is due, not to the fall in blood pressure which this drug produces, but to a dilatation of the vessels. In this respect, its effect in angina of effort is similar to that in spontaneous attacks. The extent and duration of the rise in pulse rate produced by amyl nitrite are very variable, and no general statement can be made.

The ordinary duration of pain is brief, and the shortening of the attack by amyl nitrite, though definite, is inconsiderable. In only one case was the beneficial effect greater than that of carotid sinus pressure. Several patients said that they preferred to allow attacks to pass off naturally, rather than endure the unpleasant effects of the drug. Their small consumption of freely supplied capsules confirmed this statement. It is in the

long-lasting spontaneous attacks, and especially in the type of case described by Lewis (17), that amyl nitrite gives the spectacular relief upon which its reputation rests

Nitroglycerine This drug was administered in each of the eleven cases. After satisfactory control tests had been obtained, a dose of 0.65 to 2.2 mg (1/100 to 1/33 grain) was given, and when it was fully acting on the peripheral vessels, as judged by rise in pulse rate and fall in blood pressure, a further test was undertaken. The effect on the number of efforts and on the duration of pain was recorded, and after the usual rest of fifteen minutes the test was repeated, with or without a further dose of the drug. As there is a delay of two to three minutes before the drug begins to act when given by mouth, and as the pain in most of our cases lasts less time than this, it

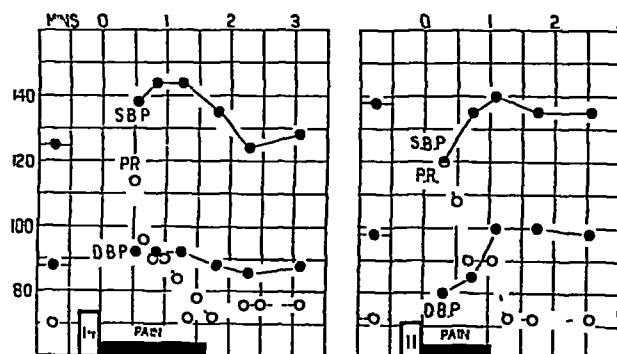


Fig 5 15432 Case 2 The chart on the left shows a control test, and that on the right, the effect of inhaling amyl nitrite immediately after exercise. The pain lasts a shorter time, and it passes off whilst the blood pressure is still rising.

is impossible to ascertain its effect on the duration of the pain by giving it after the attack has begun. In our earlier experiments we used the chocolate tablets of nitroglycerine (tab trinitrin B P 1914). It was found, however, that if they are allowed to stand exposed to the air, even for a period so short as a fortnight, they lose some of their potency. Burgess (4) notes that tablets become quite inert in time, a fact which is not yet generally appreciated. In all our later observations we, therefore, used the liquor trinitrin freshly diluted with water.

Case 1 is dealt with separately. Of the remaining ten patients, eight performed a definitely greater amount of work after nitroglycerine. The increase in the number of efforts varied considerably in the different cases. In two, even a small dose rendered it impossible to produce pain, the patient stopping from dyspnoea or fatigue after a greatly increased amount of exercise. In the others, a 30 to 150 per cent increase in the amount of exercise tolerated was produced by a dose of 1.3 mg (1/50 grain). In two

patients (Cases 2 and 3), in repeated observations and with heavy dosage, nitroglycerine was completely without effect on the number of efforts, whilst showing an unmistakable action on the pulse and blood pressure.

In general, the cases which showed the most improvement after nitroglycerine were the less severe, as judged by the amounts of exercise necessary to produce pain. Four showed a definite diminution in the duration of the pain, but this was less than with amyl nitrite, and could not be clearly demonstrated in those cases in which the pain lasted a short time in the control tests. In the two cases in which nitroglycerine failed to affect the amount of exercise necessary to produce pain, the duration of the pain was also unaffected.

Tests were made on two cases (Cases 6 and 8) to determine the duration of the beneficial action of nitroglycerine on the exercise tolerance. The effect passed off in the former, and was much diminished in the latter, 30 and 25 minutes respectively after the administration of 1.3 mg (1/50 grain) of the drug.

The pulse rate and blood pressure after nitroglycerine. In every case a dose of 1.3 mg (1/50 grain) of nitroglycerine was followed, in 2 to 4 minutes, by a definite rise in pulse rate. The systolic blood pressure fell at the same time, or a little later, by 5 to 30 mm Hg in different cases, and usually by 15 mm Hg. The diastolic blood pressure altered little, but sometimes rose a few millimetres. After exercise sufficient to produce pain the pulse rate was usually, but not always, higher than in control tests, both systolic and diastolic blood pressures were nearly always lower. In fact, in numerous observations, pain arose at a systolic blood pressure no higher than in the same patient at rest. On the other hand, in some instances, if the dose of the drug was reduced or if exercise was not begun until some time after it had been given, an increase in the number of efforts could be obtained, with no effect on the final blood pressure, the significance of this observation will be discussed later. Fig. 6 shows a typical effect of nitroglycerine on the exercise tolerated, the pulse rate, and the blood pressure.

Erythrol tetranitrate. As we have seen, the effect of nitroglycerine passes off quite rapidly. Erythrol tetranitrate is a drug of the same series with a less pronounced but more lasting dilator effect. It is widely given as a prophylactic against anginal attacks, and its reputation rests upon the impression that it reduces the frequency of attacks. We thought it of interest to determine by our tests whether this view had a real basis. A dose of 6.5 mg (1 grain) was given to nine cases, and to ensure rapid absorption, the tablets were crushed and swallowed in a draught of water. The time at which its action on the cardiovascular system becomes evident, and the extent of the changes in pulse and blood pressure brought about, are very variable from case to case. We examined its effect on the amount of exercise required to produce pain half an hour, and one hour after its administration, when some effect on pulse and blood pressure was apparent.

Only three (Cases 7, 8 and 11), of the nine cases in which it was tried, were able to perform an increased amount of work, and each of these had responded especially well to nitroglycerine. In one of these (Case 11), the pulse and blood pressure were only very slightly affected (Fig 7). Several cases which

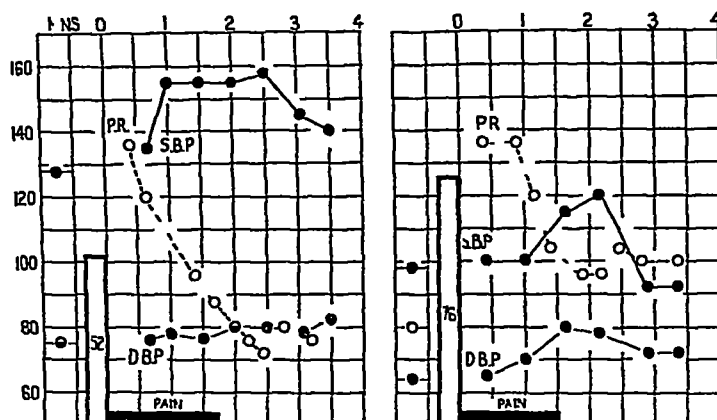


Fig 6 18 12 31 Case 6 The chart on the left shows a control test, and that on the right the effect of 1.3 mg ($\frac{1}{4}$ grain) nitroglycerine by mouth, given two minutes before exercise started. The number of efforts is increased, and the duration of the pain diminished. The blood pressure does not rise above its ordinary resting level in control tests although pain is present.

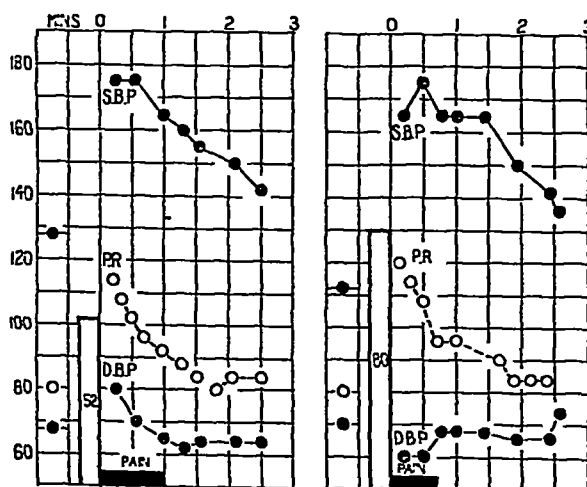


Fig 7 27 6 32 Case 11 The chart on the left shows a control test, and that on the right the effect of giving 6.5 mg (1 grain) of erythrol tetranitrate three quarters of an hour before the test. The number of efforts is increased, but there is no significant effect on blood pressure or pulse rate. The effect is not due to the long rest between tests since a further test fifteen minutes later gave an identical result.

failed to respond, however, showed alterations in pulse and blood pressure at rest comparable in extent to those after nitroglycerine, and in many the blood pressure at the onset of pain was quite as low. The duration of the pain was unaltered in every case. This drug has, therefore, a limited value in treating angina of effort. It is likely to be of value in increasing the amount of exercise which can be taken only in those cases in which this is already considerable.

A case with unusual responses to the nitrates. The reaction of Case 1 to all the nitrates differed from that of the others so much that the results must be separately recorded. The history here was suggestive of coronary thrombosis having occurred about a year before the observations began. Amyl nitrite was given four times to this patient, and, on each occasion, the duration of the pain was considerably prolonged. As a control, an inhalation of methyl salicylate, given with the suggestion that it was a

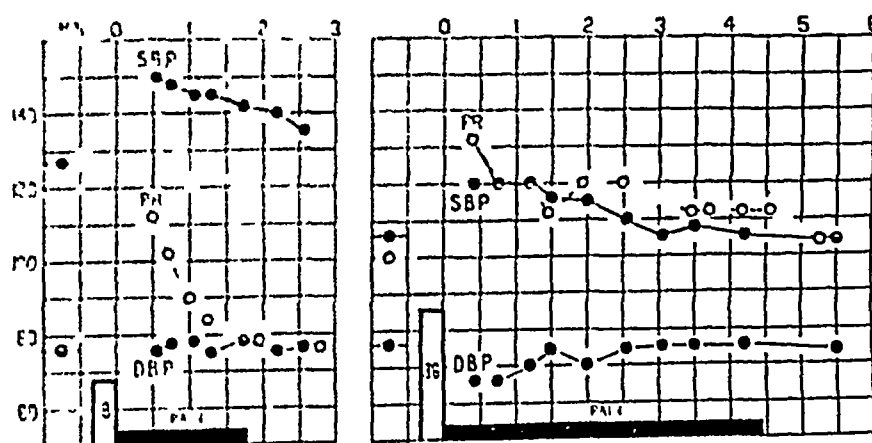


Fig. 8. 10-12-32. Case 1. The left chart shows a control test, that on the right the effect of 1 mg. ($\frac{1}{2}$ grain) of nitroglycerine, given by mouth a few minutes before exercise was begun. In this case, though the number of efforts was increased, the pain lasted considerably longer. In this patient the pulse rate remained raised for a long time after exercise whilst he was under the effect of nitroglycerine.

similar drug, had no effect. Nitroglycerine gave a moderate increase in the amount of exercise which could be taken before the onset of pain, but the pain itself was again considerably prolonged (six observations). Fig. 8 shows this effect. Erythrol tetranitrate had no effect on exercise or pain, although it reduced the blood pressure to levels similar to those found after nitroglycerine; it had, however, much less effect on the pulse rate.

Discussion on the action of the nitrates. In the first place, our results provide strong confirmatory evidence against the production of anginal pain by distension of an "irritable aorta," since, in numerous instances, when these drugs had been given, pain occurred at blood pressure levels no higher than those prevailing in the same patient at rest. We must now consider the manner in which the beneficial action of the nitrates is brought about. The

effect might be attributed either to reduction of the blood pressure, with a consequent reduction in the energy expenditure of the heart, or to an increase in the bloodflow through the coronary vessels. Our observations in the earlier part of this paper suggest that the rise in heart rate caused by nitrites would more than outweigh any advantage arising from a reduction in the blood pressure, and several facts confirm the relative unimportance of blood pressure. Thus, after amyl nitrite, the pain may pass away at a time when the blood pressure has regained a high level (Fig 5). It was pointed out that, in certain circumstances, nitroglycerine might affect the amount of exercise without altering the final blood pressure, and, in one case, a similar result was obtained after erythrol tetranitrate. This type of result is shown in Fig 7. Moreover, in cases in which nitroglycerine increased, and erythrol tetranitrate failed to increase, the amount of exercise tolerated, the effects on blood pressure were often identical. Finally, nitroglycerine failed to improve the performance in some cases in which it had a profound effect on the arterial pressure. All these facts suggest that the nitrites act by some means other than through lowering the arterial pressure. It has been repeatedly shown that the nitrites dilate, and increase the total bloodflow through, the coronary vessels of animals. Amyl nitrite is most rapid in this action, and erythrol tetranitrate is slower, nitroglycerine is intermediate in its effect (Voegtlin and Macht (27)). Where observations have been made on the intact heart, the increased flow has occurred in spite of the concomitant fall in blood pressure (Schloss (22), François-Franck (8)). It is probable, however, that such results are inapplicable to diseased and rigid coronary vessels. In the two hearts we examined after death, it was difficult to see how any agent could have caused either expansion or contraction of the occluded vessel in Case 3, and of the grossly diseased and calcified portions of the coronary artery in Case 6. Nevertheless, in both these cases, amyl nitrite diminished the duration of the pain, and in Case 6 nitroglycerine increased the number of efforts required to produce pain. Thus we believe to have been due to dilatation of the relatively healthy vessels which were also present, so that there was an increased blood supply to the ischaemic area of heart muscle. This view is supported by the following observations of Smith (23) on dogs. A distal branch of the left coronary artery was ligatured, and caused infarction of a given area. In several dogs, nitroglycerine injected into the left ventricle caused cyanosis to disappear in this area, coincident with the maximum fall in blood pressure. In other animals, and especially where the infarcted area was large, no effect could be seen after nitroglycerine. There is no doubt that, in the former cases, a dilatation of the anastomotic vessels improved the blood supply to the infarcted area. This observation suggests, in addition, that nitroglycerine might reasonably be given to cases of coronary thrombosis in the hope of reducing the size of the ischaemic area.

On the basis of these observations, we explain the effect of amyl nitrite by the increase in blood supply to an ischaemic area of the heart, either by

dilatation of the original vessels of supply, where they are healthy enough to respond or by its action on the anastomotic vessels where they are not. In two of these cases, nitroglycerine was unable to increase the bloodflow to these areas sufficiently. It is noteworthy that both gave histories suggestive of coronary thrombosis (confirmed in one case after death). Erythrol tetranitrate, though capable of dilating the relatively healthy systemic vessels, as the fall in blood pressure shows, can dilate the coronary vessels effectively when they too are only slightly diseased.

In Case 1 the action of the nitrites is more difficult to interpret, and it is reported in the hope that similar examples may be found and studied. Cases are already on record in which amyl nitrite increases anginal pain (Wood and Wolferth (31), Case 4), and we have ourselves seen a patient suffering from aortic disease with spontaneous attacks of angina, in which the inhalation of amyl nitrite would actually bring about an attack. The rise in heart rate in response to amyl nitrite and nitroglycerine was greater in Case 1 (Fig. 8) than in any other in our series, and it is probable that this factor more than outweighed any dilator effect on the coronary vessels.

Observations on euphyllin

It has long been known that caffeine and its derivatives give rise to an increased flow through coronary vessels when tested on the isolated hearts of animals. Smith, Miller and Graber (24) have compared the relative effects of different derivatives with that of nitroglycerine on the isolated heart. They found that euphyllin (theophylline ethylene-diamine) was the most potent caffeine derivative, giving, in doses comparable to a dose of 0.25 g. in man, a 40 to 90 per cent increase in the coronary flow. A similar increase was given by nitroglycerine in a dose equivalent to 0.65 mg. (1/100 grain) in man. Gilbert and Penn (9), in similar experiments, found it an efficient coronary dilator, but slightly less so than theobromine derivatives. The drug is widely employed for this purpose, and we decided to test its power of enabling our patients to perform a greater number of efforts before the onset of pain. We used for this test only patients who responded satisfactorily to nitroglycerine. Powdered tablets containing 0.2 g., given by mouth, had no effect on either pulse or blood pressure, and patients exercised at 20 and 40 minutes after the drug had been given showed no increase in the amount of exercise tolerated. We therefore resorted to intravenous administration. A 10 c.c. ampoule (0.24 g.) was given to four patients, who were tested 5 and 25 minutes after the injection. In two cases only (Cases 4 and 8), were positive results obtained. The amount of exercise tolerated increased slightly 5 minutes, and to a greater extent 25 minutes, after the drug had been given. In both these cases, however, nitroglycerine had a much greater effect. Whatever, therefore, the effect of euphyllin in animal experiments, its action as a coronary dilator is insufficient to recommend its use in angina of effort. It is to be noted in

this connection, that its clinical reputation rests mainly upon statements that its administration, over extended periods, diminishes the frequency and severity of attacks (Gilbert and Kerr (10)) The value of such evidence is notoriously difficult to assess Six of our cases have shown improvement varying in degree during the year they have been under our observation, although therapy has included little more than rest and the occasional administration of nitroglycerine Had the whole series received a prolonged course of one of the newer remedies, a false impression of its efficacy might easily have resulted It is, of course, possible that a drug which does not increase the amount of exercise tolerated in our tests, may yet give rise to clinical improvement over a period of time, or in cases other than pure angina of effort, but this appears to be unlikely

Angina of effort and aortic disease

The two cases of aortic regurgitation (Cases 4 and 5) gave results in all respects similar to those presenting no valve lesion Angina of effort is not typical of this class of case, often they suffer from the severer and spontaneous attacks described by Lewis (17) One of these (Case 5), whilst still under investigation, complained of attacks which came on in bed at night, and he could no longer be regarded as a case of angina of effort in the sense in which we have defined it There was, however, no obvious difference in the reactions of this patient to exercise after these spontaneous attacks had begun He had a positive Wassermann reaction, and it is noteworthy that the results which he gave were similar to those obtained with the others, although the coronary arteries were here probably involved mainly at their mouths, rather than lower down, as in the arteriosclerotic cases

The effect of rest on the angina of effort

Five cases spent from three to five weeks in hospital, and we were able to estimate the effect of rest on the amount of exercise required to produce pain We were surprised that the improvement was so slight The two in which the onset of the disease was recent (Cases 10 and 11), benefited most, whilst the improvement was negligible in cases of longer standing They had, of course, no attacks while they were in bed

After four months observation, Case 3 became very breathless on exertion, and complained of nocturnal attacks of paroxysmal dyspnoea He said that his attacks of angina had disappeared, and, in a test, he had to stop because of breathlessness before pain arose Congestive failure was not present He was admitted to hospital, and after a prolonged rest, a single test was made to determine the effect of exercise This showed that pain was produced by exactly the same amount of exercise as in the earlier tests During a subsequent admission to hospital, he developed congestive failure, and had no more anginal pain It is generally agreed that the onset of congestive failure causes attacks of angina pectoris to cease, and Mackenzie (19)

suggested that this is due to dyspnoea appearing during exercise before enough to induce pain has been taken. Our experience with this patient suggests that dyspnoea on exertion may occasionally protect a patient similarly, even though venous congestion has not yet appeared.

The prognosis in angina of effort

It would be unwise to generalise too widely about the progress of the disease from a study of a few cases over so short a time. We can, however, for this purpose, include a number of patients who were tested by our method on two or three occasions to determine their exercise tolerance, but who were incompletely investigated for reasons such as inadequate agreement of control tests, too great suggestibility, or insufficient co-operation. In all, there are records of twenty patients with whom we have kept in touch.

It is generally believed that the less the amount of exertion required to produce pain, the worse is the outlook. In our series this is in general true, since the cases in which pain was easily induced remained stationary or became worse, whilst improvement took place in those who already tolerated exercise well. The reason for this may be that the majority of the first group had had the disease for a year or more, whereas the latter were seen a few months after the first attack of pain.

In general, the tendency is for improvement to occur at first, probably as the result of modified habits and a greater amount of rest, followed later by a gradual diminution in the amount of exercise tolerated. In some cases, attacks eventually develop with amounts of exercise so slight that they appear to be spontaneous. Death may occur at any time, and it is noteworthy that three out of four patients who died in this series of twenty cases were able to tolerate much larger amounts of exercise than several who are still alive.

Observations are still in progress on the effect of other factors such as the taking of food, the presence of gastric distension, and the temperature of the patient's environment, which are commonly believed to influence the onset and severity of anginal pain.

SUMMARY

1 A series of eleven cases, in which exercise and exercise alone gave rise to anginal pain, has been fully investigated. In these, the amount of such exercise, in successive control tests, was found to be constant in any one case.

2 The appearance and disappearance of pain in these tests were unrelated to the height of the blood pressure, but in most cases a relation to the heart rate could be shown.

3 In four cases to which atropine was given, it caused a diminution in the amount of exercise required to produce pain, and the attack was prolonged

4 Pressure on the carotid sinus diminished the duration of pain

5 Inhalation of amyl nitrite reduced the duration of pain, but its disappearance showed no relation to the fall in blood pressure

6 After nitroglycerine, which in all but two cases increased the exercise tolerated, pain often arose at blood pressures no higher than normal

7 Erythrol tetranitrate increased the amount of exercise tolerated in three cases only, although pulse and blood pressure were usually considerably affected

8 In one case, both amyl nitrite and nitroglycerine prolonged the pain

9 In two of four patients, all of whom had responded well to nitroglycerine, intravenous euphyllin gave only a slight increase in the amount of exercise which could be taken before pain arose

10 Prolonged rest in bed had a more favourable influence on the amount of exercise tolerated in cases of recent onset than in those of longer standing

11 Our results cannot be explained on the assumption that anginal pain arises from a distended aorta. They are consistent with the view that it is due to a relative myocardial ischaemia. The rise in heart rate, which is more important than the raised blood pressure, increases the energy expenditure of the heart, without a concomitant increase in the coronary flow. The beneficial action of the nitrites in angina of effort is due to dilatation of the coronary vessels, and not to the fall in blood pressure which they produce

CASE RECORDS

We desire to express our grateful thanks to Dr Parsons Smith who introduced us to four of the patients in this series

CASE 1 F.P., a widower, aged 62, was a telephone fitter until one year ago. He smoked heavily until his present illness and is suspected to have consumed alcohol to excess

History 9 10 31 Thirteen months previously, in the course of 24 hours, he had three attacks of very severe pain in the chest, spreading to both shoulders and down both arms to the wrists. The pain lasted in the respective attacks for half an hour, an hour, and three hours, and was accompanied by great prostration. The first and third attacks occurred whilst he was at rest. The pain was much more severe than in any subsequent attack. Subsequently retrosternal pain occurred during exercise and very occasionally at rest, but for six months he has been without pain except while walking, and he knows that pain will arise after walking about half a mile on the level. When exercise ends, the pain passes off gradually. If he persists in walking the pain becomes worse, and may spread to both shoulders. It is a continuous dull 'gnawing' type of pain. It is less severe than it was six months ago and requires severer exercise to provoke it. He thinks that if he takes a nitroglycerine tablet the pain passes off more quickly. He becomes easily breathless on exertion and has a chronic cough which is worse in winter.

Summary of the results of the tests The average resting blood pressure was 100/55 and the pulse rate 68. The average number of efforts required to produce pain in the control tests was 40, and the pain lasted 1 minute and 30 seconds (18 tests). Amyl nitrite (2 tests) and carotid sinus pressure (1 test) diminished the duration of the pain. Nitroglycerine (3 tests) and erythrol tetranitrate (1 test) affected neither the number of efforts nor the duration of the pain.

Progress His pain remained unaltered, but he became breathless on exertion, and in March, 1932, began to have severe attacks of nocturnal dyspnoea during which frothy blood stained sputum was produced. The attacks were said to be very distressing, but were not accompanied by pain. He no longer had anginal pain, but his exercise tolerance was much reduced by breathlessness. He was admitted to hospital where he was free from breathlessness. The kidneys appeared to be acting normally and there were no signs of congestive failure. He improved greatly with rest, and when tested on 12.5.32, required 40 and 52 efforts to produce pain although he became more dyspnoeic than in previous tests. He went home on 13.5.32 and was readmitted on 3.6.32 with a history of similar attacks of dyspnoea. He showed Cheyne-Stokes breathing, and had 4 cm. excess filling of the veins in the neck, enlargement of the liver and slight oedema of the ankles. He developed a right pleural effusion and 1,200 ccs of fluid were removed with temporary improvement in the breathing. After morphine and hyoscine in preparation for a minor operation, he became very dyspnoeic and comatose and died after a few hours.

Post mortem findings The heart was slightly enlarged with normal valves. The descending branch of the left coronary artery was completely occluded from its origin for a distance of about 5 cm. Sections taken from the coronary arteries at various levels showed complete occlusion and calcification of this branch and considerable atheroma of the circumflex division of the left artery. The right coronary artery and its branches were more healthy, but they too, showed atheromatous changes on section. The sections of the heart muscle revealed the presence of an old infarct at the apex of the left ventricle. The remaining muscle of the two ventricles was diffusely fibrosed. The thoracic and abdominal aorta were grossly atheromatous. The pleura over the left lung showed a calcified plaque on its posterior aspect and both lungs exhibited apical scarring. The right lung was collapsed by a pleural effusion. Two small healed infarcts were found in each kidney which otherwise were normal. The basilar artery was slightly atheromatous but no signs of any alteration in the pons or medulla were evident either to the naked eye or in stained sections.

CASE 4. J.M., a married man, aged 59, is a cabinet maker, but he has not worked for several years. He used to drink and smoke heavily but does not do so now. He denies venereal infection.

History 8.12.31 He was quite well until four years ago when he began to have pain in the chest on exertion. The first attack occurred whilst walking and was extremely severe. It lasted "an hour or more" (this patient was found to be inaccurate in statements of time) and the pain recurred when he walked again. At present, walking on the flat causes similar but less severe pain, which starts in the fourth interspace to the left of the sternum, and in severe attacks passes down to the left wrist. It is "burning" in type, and leaves soreness of the chest wall behind it. It is brought on more easily after a meal and in cold weather. He says he does not become unusually breathless on exertion.

Examination He becomes more dyspnoeic than is normal on exertion. There are no signs of congestive failure. X ray and physical examination show moderate cardiac enlargement and some dilatation of the aorta. A to and fro murmur is present over the whole precordium but is louder at the base than at the apex. No thrills can be felt. The pulse is water hammer in type. The radial and retinal vessels are tortuous and thickened. There are no significant changes in the nervous system. The Wassermann reaction in repeated tests is negative, and the electrocardiogram shows no significant changes.

Summary of the results of the tests The average resting blood pressure was 140/50 and the pulse rate 80. The pain was induced by an average of 20 efforts and lasted 1 minute 30 seconds (7 tests). Amyl nitrite (1 test) reduced the duration of the pain. Nitroglycerine (2 tests) increased the number of efforts from 20 to 80. Erythrol tetranitrate (1 test) had no effect on either the exercise tolerated or on the pain. Euphyllin given intravenously (2 tests) increased the average number of efforts from 34 to 45 and diminished the duration of the pain. Carotid sinus pressure (1 test) diminished the duration of the pain.

Progress The amount of exercise required to produce pain showed little change. The attacks of angina became more frequent and very occasionally were induced by emotion. Nine months after he was first seen, he developed attacks of aching pain in the calves of the legs on walking, which passed off on resting. This pain was worse in the left than the right leg. About the same time while in bed, he began to have attacks of severe breathlessness, during which he coughed up a little blood tinged sputum. Examination showed no change in the heart or nervous system. Both posterior tibial arteries could be felt, but in the left leg pulsation was faint.

CASE 7 E T, a married man aged 68, was a gardener until his present illness

History 4 12 31 He was well until three months ago when he experienced an attack of pain in the chest whilst at work. The pain was not severe, he has had similar and more severe attacks since. It is situated behind the sternum and sometimes radiates to the left shoulder and wrist. It occurs on vigorous walking for about a mile on the flat and after a less distance up hill, and it passes off when he rests. The pain is continuous and "gripping". It is said to come more easily in cold weather and on taking exercise after a meal. He has been breathless on exertion for years. He suffers from arthritis in both knees.

Examination He shows no dyspnoea at rest but easily becomes breathless on exertion. There are no signs of congestive failure. Clinically and on X ray examination there is moderate cardiac enlargement and the aortic shadow is wider than normal. The heart sounds are normal and a faint systolic murmur is present at the apex. The radial vessels are normal, but the retinal vessels show signs of thickening. An occasional extrasystole is present at rest, and after exercise pulsus alternans and numerous extrasystoles can be detected. Both knee joints show chronic osteoarthritis.

Summary of the results of the tests The average resting blood pressure was 165/95 and the pulse rate 104. The average number of efforts required to produce pain was 50, and the pain lasted for 50 seconds (22 tests). Amyl nitrite (1 test) and carotid sinus pressure (2 tests) reduced the duration of the pain. Nitroglycerine (2 tests) and erythrol tetranitrate (2 tests) increased considerably the amount of exercise tolerated and diminished the duration of the subsequent pain.

Progress He improved considerably during a year of observation and was able to undertake much more exercise.

CASE 8 W T, is a married man aged 55, who was an engine driver until his present illness.

History 21 1 32 Four months ago he experienced pain in the chest on walking up hill rather quickly. It has since come on more easily, but otherwise has not altered. It comes on gradually, but only on exertion, and passes off when he rests. It arises after walking quickly for about a quarter of a mile on the level and after a less distance if he climbs a hill. It is situated behind the manubrium sterni and sometimes radiates to the left wrist. It is continuous, "smooth" pain or ache and the chest is sore after it has passed away. It is brought on more easily on cold damp days and by taking exercise soon after a meal. He does not easily become breathless.

Examination He does not become abnormally breathless on exertion. There are no signs of congestive failure. The heart shows neither clinical nor X ray evidence of enlargement, although the aorta is prominent. There are no signs of a valvular lesion. The rhythm is regular at rest, but when the pulse is slowing after exercise extrasystoles appear. The peripheral vessels are normal. The Wassermann reaction is negative and the electrocardiogram shows low voltage T waves in leads II and III.

Summary of the results of the tests The average resting blood pressure was 130/85 and the pulse rate 72. The average number of efforts required to produce pain was 26 and the duration of the pain 45 seconds (24 tests). Amyl nitrite (2 tests) and carotid sinus pressure (2 tests) caused a slight diminution in the duration of the pain. Nitroglycerine (4 tests) more than doubled the amount of exercise tolerated without affecting the duration of the pain. Euphyllin by mouth (0.2 g) had no effect on the exercise tolerated, euphyllin given intravenously (0.24 g) increased the number of efforts performed by 50 per cent without affecting the duration of the pain. Atropine (1 test) considerably reduced the amount of exercise tolerated and prolonged the pain.

Progress He showed a slight but steady increase in the amount of exercise required to produce pain.

CASE 9 H Z, a married man aged 51, is a boot maker by trade. He has always smoked excessively.

History 1 10 31 He was quite well until two years ago when he experienced an attack of pain in the chest on taking exercise. The pain started a little to the left of the sternum and passed down the left arm and to the back. The pain is now less severe and does not radiate. It is "burning" in character and passes away with rest leaving residual soreness of the chest wall. If he always walks very slowly no pain comes. He has had one or two attacks whilst straining at stool. He thinks nitroglycerine relieves the pain.

Examination He does not become abnormally breathless on exertion. There are no signs of congestive failure. The heart shows signs of slight enlargement. The sounds are very

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CHLORIDE AND UREA EXCRETION AS A MEASURE OF THE FUNCTIONAL ACTIVITY OF HEALTHY AND DISEASED KIDNEYS

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Introduction

It is well known that after a dose of urea by mouth, the normal individual will concentrate and excrete urea more effectively than do certain cases of renal disorder. Little attention has been paid, however, to the other changes in urinary composition which result from urea administration. It will be the object of this paper to show that in normal subjects the administration of urea increases the rate of chloride excretion in the urine, and usually increases the urinary chloride percentage, whereas it leaves these relatively uninfluenced in patients with nephritis. It will also be shown that the increases in the rate of chloride excretion, and in the percentage urinary chloride of normal subjects, are not explained by alterations in the percentage of chloride in the plasma. Furthermore, it will be shown that differences between the chloride excretion of normal subjects and that of patients with nephritis, do not depend upon differences in the plasma chloride percentage.

The maximum percentage chloride in the urine and the maximum rate of chloride excretion attained after giving urea were so frequently subnormal in tests on patients with diffuse renal disease, that an investigation was made of their value as a practical index of *slight* functional impairment of the kidneys, for while the urea concentration test of Maclean and De Wesselow is of great value, it fails to show abnormality in many cases of diffuse renal disease, and does not always demonstrate the milder defects in nitrogen excretion. It was found that this test which is concerned with the behaviour of the urinary chlorides after giving urea had the advantage that patients with almost any type of diffuse renal disease gave abnormal responses even where the urea concentration test was normal, yet cases of harmless "functional" albuminuria in adolescents gave normal reactions. Over a period of seven years this test has been found of practical value in the diagnosis of, and in determining the prognosis in cases of Bright's disease. Nevertheless some care must be exercised in the interpretation of results. As first employed (Sections 1, 2, 3) the test had the disadvantage that a

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diet deficient in chloride and perhaps also a diet containing an excess of alkali would sometimes produce an abnormal response in patients who were not sufferers from Bright's disease. Such response was most likely to occur in patients having treatment for gastric disorders. The test was, therefore, modified (Section 4) by giving urea and chloride together. This alteration overcomes the difficulty resulting from diets which are slightly deficient in chloride. In this way were combined the advantages of the Maclean-de-Wesselow urea concentration test, the De Wesselow chloride test and the first test to be described in this paper of which a brief account has been published elsewhere (9).

An attempt has been made also to explain certain features in the functional pathology of advanced chronic nephritis.

The lettering of the tests in the following tables refers to the type of patient studied and not to the form of test used. Thus Tests A 1-35 were made on subjects with no evidence of renal disease and on cases of functional albuminuria in adolescents. Tests C 1-68 were made on cases of Bright's disease. Tests B 1-10 were made on cases with renal damage not proved to be nephritis, or on cases where the patient was suffering from a condition likely to be complicated by renal damage, but in which, at the time of making the test, nephritis could not be recognised either by the symptoms, the physical signs, or by the urea concentration test.

For the purposes of this paper there was no difficulty in the subdivision of cases. Only definite cases of Bright's disease were included in the "C" group, and cases of doubtful diagnosis were classified separately until such time as it was possible to make a definite diagnosis. As "mild" cases of nephritis are often referred to it is important to explain what is meant by "mild" and upon what findings the diagnosis of Bright's disease is based in such cases.

In this paper "nephritis" includes all types of Bright's disease and does not exclude such disorders as "idiopathic nephrosis" and "amyloid nephrosis" which are said to be of a non-inflammatory nature. Using "nephrosis" in the very strict sense employed by Leiter, no case with the nephrotic syndrome uncomplicated by evidence of glomerulo-nephritis has been encountered in this series. The diagnosis of nephritis has rested largely upon the presence of a sufficient number of the following findings: albuminuria, haematuria, hypertension and oedema which is not inflammatory, obstructive, dietetic or the result of heart failure with congestion. The presence of many hyaline casts, a moderate number of granular casts or blood casts, or of any epithelial or fatty casts is taken as evidence of nephritis provided there is no other explanation of their presence.

Cases are described as mild when the patient feels well apart from slight lassitude, can produce urine containing 2 per cent. or more urea, has no more than slight transient oedema and not many red cells in the urine on microscopical examination. Several of the cases referred to could be diagnosed as nephritis or as resulting from nephritis, only by the previous history.

Method

In most of the earlier investigations the subject was starved and deprived of liquid for at least 10 hours before the urea was administered. In the subsequent tests, however, the patient was given breakfast at 5 a m consisting of one egg without salt, one or two slices of buttered toast and one cup of milk or water. This slight change in the arrangement of the test did not appear to affect the results. The bladder was emptied at 5 30 a m and at 9 30 a m. At 9 30 a m 15 g of urea dissolved in 100 c c of water were given and hourly or half-hourly urine samples were taken until 1 30 or 2 30 p m.

Urea in the urine has been estimated by the hypobromite method, which is rapid and sufficiently accurate for the purposes of this investigation, urinary chloride by the method of Volhard (3).

Plasma chlorides were estimated by the method previously described (6). The technique of blood sampling and a consideration of the sources of error and precautions which are necessary in evaluating changes in the blood composition, have been the subject of previous papers (7, 8).

Section 1 The urinary chloride before and after urea administration

In urine samples taken before any urea is given but under the standard conditions described, the chloride percentages in normal individuals usually lie between 0.3 and 0.8% NaCl according to the amount of water excreted. In cases of Bright's disease this statement holds good, but low chloride values occur much more frequently. The plasma chloride, however, is relatively constant, about 0.6% in both normal subjects and in patients with Bright's disease.

(a) *The maximum chloride percentage* In normal subjects where the dose of urea but no additional salt has been given the concentration of chloride in the urine, expressed in grams NaCl, has been found as high as 1.5%.

The maximum chloride percentage attained in the course of any test, either before or after the giving of urea, is set out in Table 1. It will be observed that a percentage greater than 0.8 is attained in 22 out of 33 tests on normal individuals, whereas in only 2 out of 65 tests* on patients with nephritis is a percentage of 0.8 or over encountered.

TABLE I

The maximum chloride percentage in urine before and after urea administration -

Total tests		Numbers attaining maximum percentage NaCl of								
		under 0 3	0 3 to 0 4	0 4 to 0 5	0 5 to 0 6	0 6 to 0 7	0 7 to 0 8	0 8 to 0 9	0 9 to 1 0	over 1 0
Normals	33	0	2	0	4	1	4	8	6	8
Nephritics	65	17	9	12	8	10	7	0	2	0

* "X out of Y tests" will be expressed in future as a fraction X/Y

TABLE
The maximum chloride percentage (as NaCl) in

Low urea concentration with edema					Low urea concentration without edema				Normal urea con with		
Case	Test	Max urea %	Max chloride	Degree of edema	Case	Test	Max urea %	Max chloride	Case	Test	Max urea %
I H	C 4	17	0.17	••	I M	C 2	13	0.29			
	C 5	17	0.50	••		C 3	13	0.17			
	C 6	15	0.61		I H	C 7	12	0.62			
					J C	C 9	10	0.72			
I L	C 18	0.97	0.19	•••					I B	C 25	23
	C 19	0.71	0.36	•••							
	C 20	0.66	0.29	•••							
I B	C 21	0.88	0.32	•••							
I B	C 22	1.2	0.50	•••							
I B	C 23	1.2	0.61	••							
K W	C 24	1.6	0.41	••							
	C 25	1.8	0.40	••							
A	C 30	0.98	0.01	••							
	C 31	1.1	0.02	••							
I W	C 32	1.5	0.51	••							
	C 33	1.8	0.48								
A W	C 39	0.7	0.43	••							
I L	C 43	0.91	0.17	••							
I H	C 44	1.9	0.24	•••							
I L	C 45	1.1	0.50	•••							
I L	C 46	1.6	0.19	••							
M O	C 49	1.1	0.19	••							
J	C 51b	1.5	0.75	••							
Y	C 56	1.28	0.43	•••							
W W	C 57	1.72	0.21	•••							
A W	C 59	0.9	0.28	••							
B C	C 62	1.7	0.61	••							
A J	C 64	0.8	0.11	••							
	C 65	0.91	0.12	••							
	C 66	1.17	0.19	••							
	C 67	0.92	0.11	••							
	C 68	1.01	0.11	••							

II

different types of Bright's disease

different types of Bright's disease

centration oedema		Normal urea concentration without oedema				Subsequent progress	
Max chlorido	Degree of oedema	Case	Test	Max uron %	Max chlorido		
0 55	*	J C	C 8	2 3	0 64	Died within a few weeks of C 3	
			C 10	2 0	0 63	Moderately well 7½ years after C 4	
			C 11	2 4	0 71	Perfectly well 7½ years after C 9—working normally throughout	
			A B	C 14	2 2	0 91	Died a few months after C 14 from other causes
				C 17	2 2	0 68	Died a few months after C 18
		K.W	C.29	2 2	0 56	Died about 5 months after C 21	
						7½ years after C 22 is poorly and shows marked functional impairment	
						6½ years after C 27 feels very well and a functional test shows no abnormality and there is no albumin in the urine	
						Died within a few weeks of C 30	
						6½ years after C 33 feels perfectly well—no intervening illnesses	
0 40	**	F W	C 35	2 0	0 59	Is well and has had no further trouble since C 32, 6½ years ago	
			I G	C 32	2 1	0 62	Is moderately well 6 years after C 36, there is occasional oedema
		N O	C 36	2 7	0 99	Is well 6 years after C 38 and a further renal function test shows no abnormalities and the urine is free from albumin	
			C 37	2 4	0 73	Died within a few weeks	
		F.Mo	C 40	2 1	0 75	Is moderately well 6 years after C 40, works and plays golf	
						Died within a few months of C 41	
		0 45	***				Died a few months after C 42
							Died a few weeks after C 43
		0 57	**				Died within a few months of C 44
							Died about 4½ years after C 46
0 47	**	W	C 55	2 6	0 71	Died within a few weeks of C 47	
0 63	*					Died within a few weeks of C 48	
						Died within a few months of C 49	
						Feels well and is working 5 years after C 50	
						Died with an acute recurrence Date unknown	
						Quite recovered and free from albumin 5 years after	
						Is working as a nurse 5 years after but has much albuminuria	
						Died (date unknown)	
						Died (date unknown)	
0 48	**					J H	C 60
		N e	C 61	2 8	0 46	Fit and well 5 years after C 53	
						Died within a few weeks of C 59	
						Moderately well Main complaints non renal 4½ years after C 62	
						Moderately well Almost normal activity 7½ years after C 64	

*** Very marked oedema not necessarily universal

**** Gross generalised oedema.

The maximum urinary chloride percentage attained after a dose of urea is not, however, the highest urinary chloride percentage which can be attained, for if chloride is administered alone, (de Wesselow 1925 (10)) or in addition to urea (Section 4 of this paper) higher chloride percentages are found in the urine

In regard to the amounts of salt contained in their diets, there was no gross or consistent difference between the normal subjects and the patients with nephritis. It must be emphasised, however, that the amounts of salt stored in the blood and tissues may be unequal in subjects receiving approximately similar diets (11), for in addition to the amounts of salt consumed, the renal and extra renal excretions are to be considered, as also the possibility that the tissues in unhealthy subjects may have intrinsic changes in their mineral metabolism. Amounts of salt which are well excreted by normal subjects are said to be retained without œdema formation in cases of "chronic interstitial nephritis" (2)

The danger of misinterpretation comes when the chloride reserves are depleted, which may follow either an inadequate supply of salt in the diet or the loss of salt by vomiting. Again, if there is a rapid accumulation of œdema the salt concentration of body fluids may fall by dilution unless additional salt is retained.

If we consider now the maximum chloride percentages attained after giving urea to patients with different types of Bright's disease it will be observed (Table 2) that the highest chloride percentages usually occur in tests where the urea concentration is 2% or more, and particularly in those patients who have no œdema at the time of the test. Where the urea concentration is 1.4% or less the maximum chloride concentration after giving urea is low both in patients with and without œdema, and is usually less than 0.5%. Chloride percentages in the urine higher than the chloride percentage in the blood (0.6) are usually associated with a normal urea concentration and do appear to indicate a good prognosis (Table 2) if we except such accidents as recurrent attacks of acute nephritis, to which there is a greater susceptibility when a renal lesion is already present.

(b) *The increase in the percentage concentration and rate of excretion of chloride when urea is given by mouth.* In most experiments upon normal subjects where the initial urinary chloride percentage is low (say 0.6% or less) urea has caused an increase of 0.2 in the urinary chloride percentage (Fig 7).^{*} If the percentage is already high (say 0.6 or more) there may be no further increase in percentage (Fig 8), but only an increase in the rate of chloride excretion; and also, if there is much increase in the rate of urine formation the percentage chloride may fall. In tests on patients with nephritis even when the initial urinary chloride percentage is low, urea seldom causes an increase in percentage of 0.2 or more (Figs 9, 11 and 12). Likewise the increase in the rate of chloride excretion is not usually as great as 0.2 g. per hr

^{*} For Figs 7—12 see pages 152 and 154

It is of fundamental importance to know whether in Bright's disease this subnormal degree of increase in the rate of chloride excretion and in the percentage of chloride in the urine (after urea) is directly the result of disease in the kidneys, or is due to a reduction in the chloride reserves

For this reason a comparison is made of the responses of normal and nephritic subjects showing the same initial rates of chloride excretion (Table 3) the same initial percentage of chloride in the urine (Table 4)

TABLE III

A comparison of the increases in the rates of chloride excretion after giving urea, in normal subjects and patients with nephritis whose initial rates of chloride excretion were equal before urea was given

Initial rate of chloride excretion before urea (g per hr)		0 0 to 0 1	0 1 to 0 2	0 2 to 0 3	0 3 to 0 4	0 4 to 0 5	0 5 to 0 6
Normal subjects	Number of tests	3	8	10	4	6	1
	Number of tests with increase of less than 0.2 g per hr	0	1	3	0	1	0
	Average increase (g per hr)	0.58	0.35	0.55	0.42	0.34	0.23
Patients with nephritis	Number of tests	11	15	12	9	3	2
	Number of tests with increase of less than 0.2 g per hr	11	9	6	5	1	2
	Average increase (g per hour)	0.06	0.19	0.17	0.22	0.42	0.13

TABLE IV

A comparison of the increases in the percentage urinary chloride after giving urea in normal subjects and patients with nephritis whose initial percentage chlorides were equal before urea was given

Initial percentage chloride before giving urea (g per 100 c c)		0 0 to 0 1	0 1 to 0 2	0 2 to 0 3	0 3 to 0 4	0 4 to 0 5	0 5 to 0 6	0 6 to 0 7	0 7 to 0 8	0 8 to 0 9	over 0 9
Normal subjects	Number of tests	2	1	2	3	3	4	6	2	6	4
	Number of tests with increase of less than 0.2 per cent in the chloride	0	1	0	1	0	2	4	1	3	3
	Average increase in the chloride (per cent)	0.61	0.15	0.43	0.39	0.43	0.11	0.11	0.09	0.13	0.02
Patients with nephritis	Number of tests	3	11	7	11	6	13	4	3	0	0
	Number of tests with increase of less than 0.2 per cent in the chloride	3	8	7	10	6	12	4	3	—	—
	Average increase in the chloride (per cent)	-0.01	0.13	0.02	0.05	0.03	0.00	-0.07	-0.05	—	—

and the same plasma chloride (Section 1d) It will be seen that, even when they start with the same initial rates of chloride excretion, the normal subjects show a more marked increase in chloride excretion after taking urea, than do patients with Bright's disease Also normal subjects and patients with Bright's disease having the same initial percentage chloride in the urine, show differences in their powers to increase further the chloride percentage

The effect of urea upon the urinary chloride percentage depends upon the severity of the nephritis as judged by the maximum urea percentage When the maximum urea concentration is 1.4% or less the increase in the chloride percentage is usually less than 0.06% and in only 4/22 tests has it been more than 0.1% but in patients where the urinary urea concentration is normal the increase in percentage chloride though seldom as much as 0.2% was more than 0.1% in 9/18 tests In Bright's disease with a low urea concentration the concentration of chlorides in the urine is as a rule less than in patients with a normal concentrating power for urea

(c) The maximum urinary chloride percentage after giving urea in cases of Bright's disease where the capacity to concentrate urea is normal

The cases which ordinarily give difficulty in diagnosis are those where the urea concentration attains 2% or more The practical value of chloride estimations in the course of a urea concentration test is well demonstrated in such patients The maximum chloride percentages in normal subjects and patients with nephritis are given in Tables 1 and 2, and the maximum urea percentages in Fig. 2

A concentration of more than 0.8% NaCl has been attained in 22/33 tests on normal subjects and in only 2/21 tests on subjects with nephritis A further separation may be effected if together with the maximum percentage NaCl attained, we consider that, although the urea concentration is above 2% in this group of patients yet it reaches 2.5% in only 6/24 tests, whereas in normals this percentage is reached in 29/33 tests

(d) The relationship between the percentages of chloride in the plasma and the excretion of chloride in the urine after giving urea It has been suggested that the increased chloride output which follows the administration of many diuretics is the result of the mobilisation of chloride from the tissues and the excretion by the kidneys of this excess in the plasma

In Table 5 it will be seen that the plasma chloride percentage both of normal subjects and patients with nephritis is only slightly influenced by giving urea Variations which occur are usually within a range of 0.02 g per 100 c.c. of plasma Such changes are usually in the direction of decrease and although small in degree they are often greater than the chemical error In the analysis of a single sample the chemical error is less than + 0.005 g per 100 c.c. of plasma Estimations were made in duplicate or triplicate.

TABLE V

Examples illustrating that changes in the urinary chloride after giving urea do not depend upon changes in the plasma chloride percentage

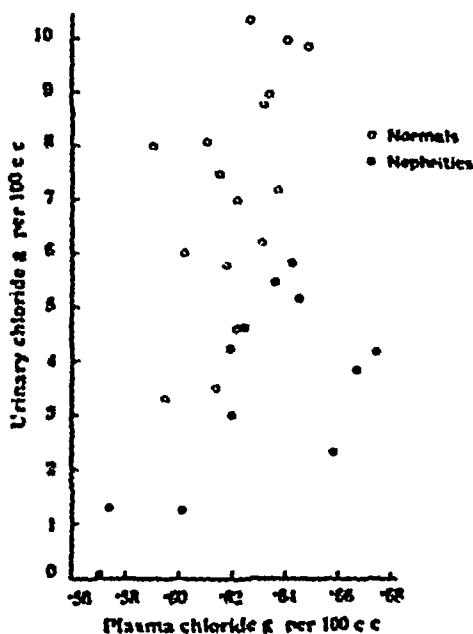
	Change in plasma chloride (%)	Change in rate of chloride excretion (g per hr)	Change in urinary chloride (%)
Normal subjects	-0.012	+0.92	+0.50
	-0.016	+0.52	+0.72
	-0.031	+0.32	-0.19
	-0.018	+0.43	-0.30
	+0.006	+0.33	+0.16
	+0.005	+0.37	-0.22
Patients with nephritis	-0.017	+0.12	+0.02
	-0.029	+0.10	+0.05
	-0.010	+0.17	-0.08
	-0.013	+0.06	-0.15
	+0.014	-0.09	-0.19
	+0.003	-0.15	-0.22

From the results of 21 tests on normal subjects and 21 tests on patients with nephritis it is clear that in both, comparatively large changes in the rate of the chloride excretion, and in the percentage chloride of the urine, may take place without there being any corresponding change in the plasma chloride, and the chlorides of the urine may increase while the plasma chloride falls. The changes in the plasma chloride are in any case small (usually less than 0.02%) compared with the urinary changes which may be ten to sixty times as large. It is not suggested that small changes in the plasma chloride have no influence upon the urinary chloride but in these experiments the influence of this factor is not dominant.

Although changes in the percentage chloride in the urine after giving urea are not dependent on changes in the plasma chloride percentage it is of interest to know whether the percentage urinary chloride is the same in normal subjects and in patients with nephritis whose plasma chloride percentages are equal. There is, however, some difficulty in deciding which value of the urinary chloride is to be selected as representative of a particular experiment. The maximum chloride percentage after giving urea has been chosen for this purpose because in this there is usually a clear distinction between the chloride concentrating powers of normal subjects and patients with nephritis. The plasma chloride percentage corresponds with the maximum chloride percentage after giving urea in time relation.

It will be seen from Fig. 1 that for equal values of the plasma chloride the urine of normal individuals has a much greater concentration of chloride than that of patients with Bright's disease. It is clear, therefore, that in the majority of these experiments the relatively low chloride concentration

attained in cases of nephritis cannot be attributed to a relative deficiency of chlorine in the plasma—the probable consequence of a diet poor in salt. In two experiments, however, the presence of a percentage of chloride in the plasma below 0.58% is in itself sufficient explanation of the low urinary chloride. To what degree chloride may be stored in, or removed from, depots such as the skin without alteration in the plasma chloride is a matter outside the scope of the present paper, but a relatively high plasma chloride in the patients with Bright's disease may be taken as contributory evidence that an adequate supply of chloride is available. It is of interest to compare the above results with those obtained by De Wesselow after giving chloride. De Wesselow (10) found that the urinary chloride concentration of normal



the heavy protein losses in the urine. For if by ultrafiltration "in vitro" we remove some of the plasma proteins, then the filtrate will have a higher proportion of salts owing to the removal of the large protein molecules.

Section 2 The urinary and blood urea

So far this paper has dealt with the significance of the maximum chloride percentage and the increase in chloride excretion which may occur after giving urea. It has been shown that the behaviour of the urinary chlorides after giving urea, betrays alterations in the functioning of slightly abnormal kidneys which are nevertheless, able to concentrate urea normally.

It now remains to consider the percentages of urea in the blood and urine, since these are of recognised value in determining the prognosis of relatively advanced cases, and with them another factor, the total amount of urea excreted by the kidneys during the 4 or 5 hours after urea administration.

(a) *The maximum urea percentage in the urine* The maximum urinary urea percentage during the 5 hours after urea administration is not necessarily the same in successive tests upon the same subject even supposing the general condition of the subject remains unchanged. Variations of as much as 0.4 in the maximum urea percentage between successive concentration tests are encountered and a patient with a percentage of 2.2 at first may have 1.8 or 1.9% on a second examination. These changes are often attributable to variations in the water output.

In both normal subjects and patients with nephritis the maximum urea percentage does not usually occur in the first 3 hourly samples after taking the urea. This delay in reaching the maximum urea concentration may account for the fact that higher concentrations are usually recorded by the Calvert than by the Maclean technique. If the attainment of a 2% concentration of urea is to be used as an index of good prognosis it is of importance to consider the way in which the test is arranged. In 29 normal subjects in which hourly urine samples were taken for 4 or 5 hours after giving urea the maximum urea percentages were attained as follows —

17 times in the 4th or 5th hours				
5	"	"	"	3rd hour
5	"	"	"	2nd "
2	"	"	"	1st "
and in 59 tests on subjects with nephritis,				
25 times in the 4th or 5th hours				
15	"	"	"	3rd hour
16	"	"	"	2nd "
3	"	"	"	1st "

Although there are many patients with nephritis who attain a concentration of 2% or more urea in the urine yet the number of these who reach

2.5% is very much smaller. In most cases of Bright's disease where urea concentrations of over 2.5% have been encountered, it appears that these have occurred at the expense of the chloride excretion.

On Fig. 2 are compared the maximum urinary urea percentages found in the course of 61 tests on patients with nephritis and 32 on normal subjects. Although a 2% concentration is attained in 26/61 tests on subjects with nephritis only 8 of these reach a concentration of 2.5% whereas in 29/32 tests on normal individuals this percentage concentration is attained. It will be seen (Fig. 2) that in the patients with nephritis who attain a urinary urea percentage of 2.5, the corresponding chloride concentrations in the

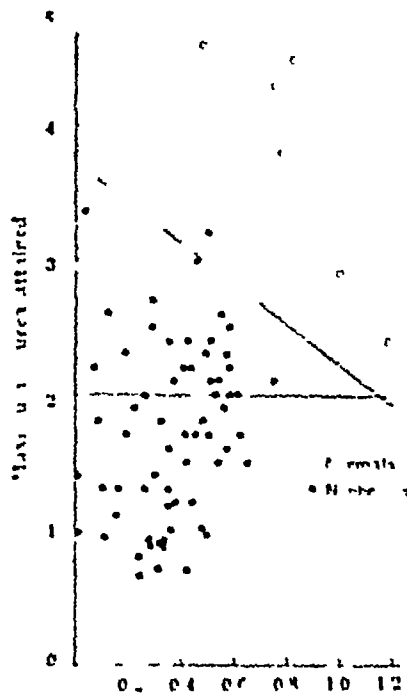


Fig. 2. Relationship between the maximum percentage of urea in the urine sample with the maximum chloride percentage in the urine sample containing the maximum urea percentage.

Fig. 2. The relationship between the maximum percentage of urea in the urine after giving urea and the chloride percentage in the urine sample containing the maximum urea percentage.

urine are generally much less than in normal individuals with similar urea concentrations. It seems very probable that the presence of a low percentage chloride and a diminished rate of urine formation, enables the damaged kidney to form a higher urea percentage in the urine than would be possible if the urinary chloride percentage and the rate of urine formation were normal. On Fig. 3 are plotted the rates of urine formation corresponding in the patients with nephritis to all the urea percentages over 2%. Practically all the points on the diagram which represent samples of urine from cases with nephritis fall within the area shown.

Although some of the samples of urine from normal subjects have urea percentages and rates of urine formation which would fall within the nephritis area, in at least one sample in almost all normal tests the urea percentage and rate of urine formation are such that they fall outside the

circumscribed area on Fig 3 In practically every case of nephritis there appears to be some defect in the excreting power of the kidneys for urea when compared with the large majority of normal subjects

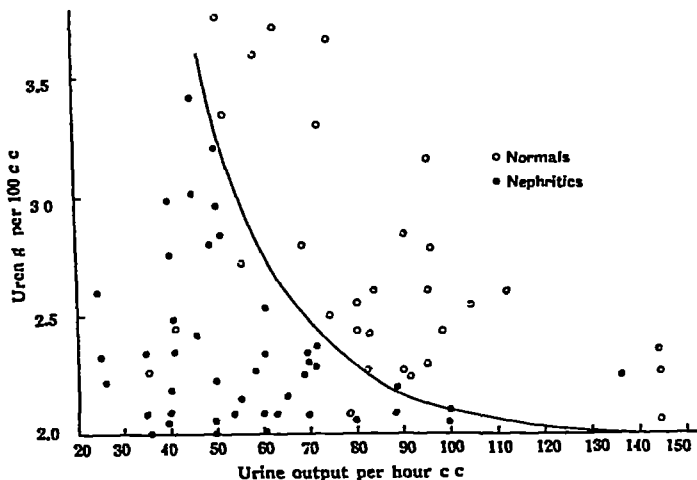


Fig 3 The relationship between the rates of urine formation and the percentages of urea in the urine after giving urea

(b) *The total urea excreted* The amount of urea excreted in the 4 or 5 hours after urea administration has been followed in relation to the blood urea and to the subsequent progress of the patient. When the total amount of urea excreted in a period of 4 or 5 hours is diminished to below 3 g, there is often an increase in the resting level of the blood urea. This is not an invariable finding since, despite the diminished rate of urea excretion, the blood urea may be low because there is little protein in the diet. In such a case an increase in the protein content of the diet would raise the blood urea. Conversely patients with a blood urea of 50 or 60 mg per 100 cc of blood may excrete administered urea without difficulty, as though the renal mechanism remained sensitive to concentrations of urea in the blood lying above this level (C9, C10, C11, Fig 9)

The total urea excreted is of some value in prognosis. Thus if the maximum urinary urea percentage after giving urea is low the prognosis of the case is not so bad if the amount of administered urea excreted within 4 hours is approximately normal. In other words prognosis is better where any compensatory diuresis present is sufficient for the excretion of the metabolic products.

As a rule when 5 or more grams out of the 15 are excreted during the 4 hours after giving urea there is no change in the resting level of the blood urea percentage. If, however, 3 g or less are excreted there is almost always urea retention unless the protein intake is limited strictly.

For example J M (C 1, C 2, C 3, Fig 12) when admitted to hospital had a maximum urinary urea concentration of 11 and was excreting

1.3 g of urea during the 5 hours test. A fortnight later his maximum urinary urea concentration was 1.3, but the excretion of urea was only 2.8 g owing to a fall in water excretion from 437 to 235 c.c. The blood urea was then found to be 304 and death took place 21 days later.

A. W. (C 39) had a urinary urea concentration of 0.7 and excreted 2.1 g of urea in three and a half hours, her blood urea was 300 mg % and she died within a fortnight. The urinary output of 315 c.c. in three and a half hours was inadequate.

J. L. (C 18, C 19, C 20) in contrast had urinary urea concentrations of 0.97 and 0.71 and excreted 5.7 g of urea in each 5 hours test. The urinary output of 675 and 913 c.c. provided an almost adequate compensation for the low percentage of urea in the urine, hence the blood urea was only 42 and 48 mg and the patient felt relatively well. Later the urea concentration fell to 0.66 and the urinary output of 602 c.c. became inadequate so that the urea excretion fell to 2.6 g in the 5 hours. The patient at this stage was uræmic and died some months later. Again A. H. had urea concentrations of 1.5 and 1.1. His urinary output of 672 and 760 c.c. enabled 7.7 g of urea to be excreted in the 5 hours. He was alive, moderately well and following his occupation two and a half years later.

A. J. (C 67, Fig. 11) when in hospital had a urinary urea concentration of 0.91, but owing to a diuresis of 881 c.c. he was able to excrete 6.9 g of urea in 5 hours. His blood urea was 50 and 58 mg on two occasions. Since leaving hospital the patient has played football. On re-examination 2 years after leaving hospital, the patient mentioned an increase in lassitude, and there was more œdema under the eyes. The urea concentration was 0.92% and only 3.0 g of urea were excreted in 4 hours with a urinary output of 517 c.c. The corresponding blood urea was 68 mg. Since then the patient has improved again and 7 years later is feeling quite well. The systolic blood pressure is 140.

The amount of urea excreted in a given period (3, 4 or 5 hours) appears to be of almost equal value to the blood urea percentage in estimating the severity of a renal function defect, and might be of greater value if the dose of urea given was in proportion to the body weight or perhaps to the body surface.

(c) *The clinical significance of fixation of the urinary urea percentage or of a fall in this percentage after giving urea.* It is interesting to observe that in not a few cases of nephritis the urea percentage may actually fall (C 3, Fig. 12, C 9, C 10, C 27, C 43, C 56) or may rise by less than 0.2% (C 1, C 2, C 19, C 37, C 39, C 48, C 51, C 57, C 59) after the administration of urea.

The blood urea was estimated on the subjects of some of these tests. (In C 1, C 2, C 3 and C 39) the blood urea was over 300 mg %. In C 56, and C 59 it was between 90 and 130, in C 9 and C 10 it varied between 66 and 77 and in C 19 and C 57 it lay between 42 and 48. In only 1 test C 27, was the blood urea definitely normal.

The fixation of the urea % at a low level is usually accompanied by a fixation of the chloride percentage. The urea fixation is partly explained by the fact that the blood urea is high and the addition of 15 g makes less proportional difference to the urea content of the blood. In addition the kidneys usually are working at or near their full functional capacity. In many cases the kidney produces a urine with a similar osmotic pressure to that of blood the slight remaining power to raise the concentration of urea in the urine above that in the plasma being associated with a fall in the percentage urinary chloride below that in plasma.

It will be seen from Table 2 that 9/12 of these patients with fixation of the urinary urea % died, mostly within a few months of the date of performing the test. In all but one of the patients who died the capacity to concentrate urea was impaired seriously. In the 3 patients who improved the maximum urea percentage was above 2 in 2 cases and was 1.6 in the remaining case.

Section 3 The relationship between the excretion of chloride and of urea in the urine. The value of the expression $C + \frac{U}{2}$, and an hypothesis which endeavours to explain the functional pathology of advanced chronic nephritis

(a) *The relationship between the percentages of urea and chloride in the urine.* In cases of Bright's disease it is observed very frequently that throughout a 5 hour test each increase or decrease in the concentration of urea is accompanied by a decrease or increase in the concentration of chloride. On the other hand such inverse relationships between the urea and chloride percentages are uncommon in normal subjects.

For example in 18 consecutive urine samples collected in the course of tests C 9, C 10, and C 11 (Fig 9), which were performed on the same subject, every increase or decrease in the urinary urea percentage has been accompanied by a decrease or increase in the percentage chloride, of a magnitude proportional to the degree of change in the percentage of urea. The response in C 10 is exactly the same as in C 9 except that a large diuresis at the second hour has caused a slight fall in the urea and chloride curves. In both C 9 and C 10 the urinary percentage of urea fell after giving urea. In C 11 (Fig 9) the percentage of urea in the urine increased owing to the absence of the diuresis present in C 9 and C 10 but the inverse relationship of the chloride to the urea was still evident. Such inverse relationships are not observed in normal subjects (A 1, Fig 7, A 20, Fig 8).

Again it will be noted that in tests where the urea percentage maintains an almost constant concentration throughout the test, it is usual for the chloride concentration similarly to be fixed as in C 3 (Fig 12), C 43, C 54, and C 65 (Fig 11). An exception to this rule is C 27. It is evident that whereas no difficulty is experienced by the normal kidney in increasing simultaneously the concentrations of urea and chloride in the urine, a considerable simultaneous increase in the percentages of urea and chloride is comparatively rare in patients with Bright's disease, the only clear instance being illustrated in Fig 10, and this was a rather mild case.

From Fig 2 it will be seen that in the samples where the maximum urea percentage has been reached, the chloride is almost always lower in patients with nephritis than in normal subjects having the same urea percentage. The line drawn at 45° across Fig 2 practically divides the normals from the cases of Bright's disease. One normal alone seems to constitute a serious exception and deserves special mention. The subject of this test was admitted for gastric ulcer, neither in the history nor in the physical examination was there anything to suggest renal disease and the patient was selected as a normal control. The first urine sample passed on the morning of the test gave a cloud with salicyl sulphonic acid which appeared on further examination to be due to mucin. No albumen or globulin were detected in this sample or in subsequent samples. The abnormal response was probably explained by heavy doses of alkali which the patient was taking for her gastric condition. It has been shown, (4), that the chloride excretion in the urine is depressed by heavy doses of sodium bicarbonate. In support of this suggestion it may be mentioned that several of the "normals" lying near the border-line were gastro duodenal cases taking heavy doses of alkali.

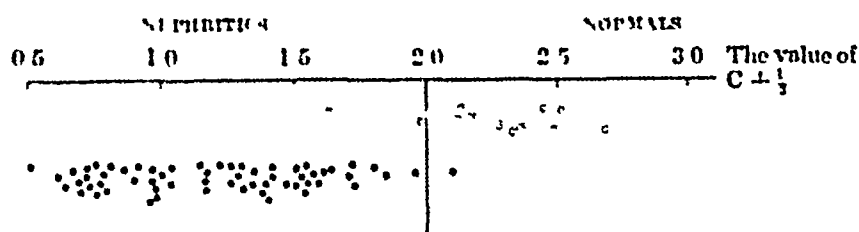


FIG. 4. The value of the expression $C + \frac{1}{2}$.

(b) *The significance of the expression $C + \frac{1}{2}$.* From the relationships between the chloride and urea excretion in Fig 2, it can be shown that, where U is the maximum urea percentage and C is the chloride concentration of the urine sample in which this maximum urea percentage was attained (expressed in g NaCl per 100 c.c. urine) then the expression $C + \frac{U}{2}$ is greater than 2 in practically all normal subjects and less than 2 in practically all cases of Bright's disease. The values of this expression in all normal and nephritic subjects investigated are represented in Fig 4.

In the various charts of individual tests (Figs 7-12) the scale used is such that the value of this expression for any urine sample can be seen at a glance. If the mid point is taken between the urea and chloride percentages and the position of this point read off on the vertical scale for urea, the figure obtained is the value of the expression $C + \frac{U}{2}$.

As the chloride and urea percentages tend to vary inversely in tests on cases of nephritis it follows that the value of $C + \frac{U}{2}$ is relatively unaltered in the course of these tests. On the other hand in normal subjects the values of this expression are not only greater than the values obtained in patients with nephritis, but often they are increased considerably after giving urea.

The value of the expression $C + \frac{U}{2}$ in the course of the ordinary urea concentration test described appears to be the most accurate indication of the presence of mild grades of renal damage

It is of interest to note that as the molecular weights of urea and sodium chloride are practically equal, the osmotic pressure of the urine due to urea and chloride will be equal to $k(C + \frac{U}{2})$ where k is a constant

In 3 patients with no evidence of any renal lesion but where the chloride content of the diet was known to be low the values of $C + \frac{U}{2}$ were all sub-normal, namely 1.68, 1.62, and 1.92. The first two of these subjects were receiving sodium bicarbonate as treatment for their gastric conditions, and this is liable to decrease further the urinary chloride excretion

In patients with serious defects in the power to concentrate urea the osmotic pressure of the urine may be little or no greater than that of the blood, for although the urinary urea is greater than the blood urea it is found, almost invariably, that the urinary chloride is less than the plasma chloride. This is a very remarkable thing for the most severely damaged kidneys would appear theoretically to be performing more work *in respect of the chlorides* than do most normal kidneys. The minimum work done is not to be confused, however, with the energy expended and it may be that the efficiency of the damaged kidney is greater when the degree of osmotic pressure difference between plasma and urine is diminished by a fall in the urinary chloride percentage

(c) *A theory concerning the functional pathology in cases of severe chronic nephritis where the capacity to concentrate urea is markedly impaired.* The following explanation is thought to be consistent with all and may explain some of the results described in Sections 1, 2 and 3

Let us suppose that somewhere inside the renal tubules the urea is concentrated locally, by the activity of the relatively healthy cells, to above the percentage of urea contained in the plasma

It is of no account whether the concentration takes place by the re-absorption of fluid from the glomerular filtrate or by the secretion of urea into it. It may be assumed, however, that the saline concentration of the glomerular filtrate is about the same as that of plasma ultra filtrate

The total osmotic pressure of the tubular urine is therefore, increased. It is suggested that the tubular urine is unable to maintain this molecular-ionic concentration because of the presence of damaged tubule cells which are unable to prevent the diffusion of water from the blood into tubular urine containing a higher molecular-ionic concentration of dissolved substances. If most of the active renal tubules are so affected, and the degree of damage to the individual tubules is sufficiently great, this diffusion of water may continue until the total osmotic pressures of blood and tubular urine are equal as in advanced chronic nephritis. In this way the polyuria and the fixity of the molecular ionic concentration of the urine at about that of plasma are explained and probably also the independence of the urine composition and the rate of urine formation

Verney (12), while giving emphasis to the inherent difficulties of the problem, compared the polyuria of advanced nephritis in which the amount of active tissue is reduced by disease, with the polyuria of kidneys in which the amount of active tissue has been reduced by tissue extirpation or by the ligation of vessels. As a result of these procedures the kidneys are said to secrete "a more copious urine and one which approaches towards the plasma in its composition." In regard to the chloride percentage, however, the composition of the urine in the polyuria of advanced nephritis never approaches but always recedes from that of the plasma. The analogies which are also drawn between the urinary composition in advanced nephritis with polyuria and the composition of urine from isolated kidneys poisoned with potassium cyanide or asphyxiated temporarily by occlusion of the renal artery or by a cessation of artificial respiration are also misleading, for a similar reason.

It appears that the changes in the urinary composition which result from the processes of disease differ widely from those observed in experimental reduction of the amount of active tissue in the kidney, and although in advanced nephritis many renal tubule cells without doubt receive an inadequate supply of blood, the effect upon urine composition is not very similar to that produced by asphyxia.

The hypothesis of "re-dilution of the tubular urine by water diffusion" explains the fall in the chloride percentage as well as the polyuria. The chloride dilution may be explained entirely by dilution, no work being done, upon the chloride, or, there may be in addition to this an active re-absorption of chloride from the tubular urine. Re-absorption of chloride would increase the urea concentrating efficiency of the damaged kidney for, by diminishing the osmotic pressure of the tubular urine and thus limiting the diffusion of water through damaged cells into the lumen of the tubule it would enable a higher percentage of urea to be maintained.

By calculation from Hill's formula (5) it can be shown that the additional work done in diminishing the percentage of chloride in the tubular urine below that in the plasma, is much less than the work done on the urea* which, according to this hypothesis, would be dissipated by the unresisted diffusion of water into the tubular urine.

It is suggested also that diffusion of water into the tubular urine explains the inverse relationship between the percentages of chloride and urea in the urine of advanced cases of nephritis. For such diffusion will tend only to equalise the molecular-ionic concentrations in the urine and plasma and therefore an increase or decrease in the concentration of either constituent will be accompanied by a relative decrease or increase in the concentration of the other.

* My thanks are here due to Professors Donnan and A. V. Hill for their kindness in discussing with me the calculation of the minimum work done by the kidney.

Again the hypothesis may explain why, despite the fact that the urine is already dilute in such cases, it is not possible to render it more dilute by water drinking, for, if by the activity of the relatively healthy tubule cells the tubular urine is rendered hypotonic, the diffusion of water back through the damaged cells into the blood would tend to maintain the total osmotic pressure of the urine at about that of the blood.

It is not considered, however, that diffusion of water into and out of the tubular urine is the only factor which influences the changes in the composition and flow of urine which could be explained in terms of this hypothesis.

Section 4 The effect of administering 3 grams of potassium chloride and 13 grams of urea to normal subjects and to patients with nephritis

The test with urea alone, but including the estimation of chlorides as well as urea in the urine, has been found to be a most sensitive biochemical test for the presence of mild grades of functional damage to the kidneys. It is important, however, that the subject of the test should not have been on a diet poor in salt, otherwise abnormal responses may be obtained in normal subjects.

The object of the test described in this section is not to improve the selectivity so much as to simplify arrangement and to enable the same information to be obtained by the analysis of fewer urine samples, while reducing the difficulties caused by diets poor in salt.

The results were obtained by administering instead of urea a mixture containing both potassium chloride and urea.

Standard routine The subjects of this test are deprived of fluid overnight and are given a breakfast consisting of one egg, one slice of toast or bread with butter, and six ounces of milk or water but not tea. Two hours later the bladder is emptied and a mixture of 3 g of potassium chloride and 13 g of urea dissolved in 100 cc of water are taken by mouth. The patient next empties the bladder two hours after taking the mixture and again one hour after this. The volumes of urine passed are measured and the chloride and urea percentages estimated by the methods already referred to on page 133.

Results The results obtained are summarised briefly in Figs 5 and 6. On Fig 5 the result of each separate test is represented by a single point. The height of the point above the base line represents the maximum percentage of chloride attained in the two samples of urine and the distance along the abscissa represents the total amount of chloride excreted in the whole three hour sample of urine. It will be seen that in only 5/22 patients with Bright's disease does the chloride concentration rise as high as 0.8% and in 2 of these the high concentration appears to be attained at the expense of the urinary output. All 5 patients with chloride concentrations over 0.8% were very mild cases. It must be remembered, however, that in patients with nephritis chloride concentrations over 0.8 were obtained.

with greater frequency by De Wesselow (1925) when 4 g of potassium chloride was given alone and the patient deprived of water

On Fig 6 the ordinates represent the maximum urinary urea percentage attained during the test and the abscissæ represent the total urea excreted in the 3 hour sample. It will be seen that in practically all cases where the urea percentage of a patient with Bright's disease is above 2, it appears to be because the urinary output is low and in consequence the total urea excreted is, in such cases, less than in normal subjects with the same urea concentrations

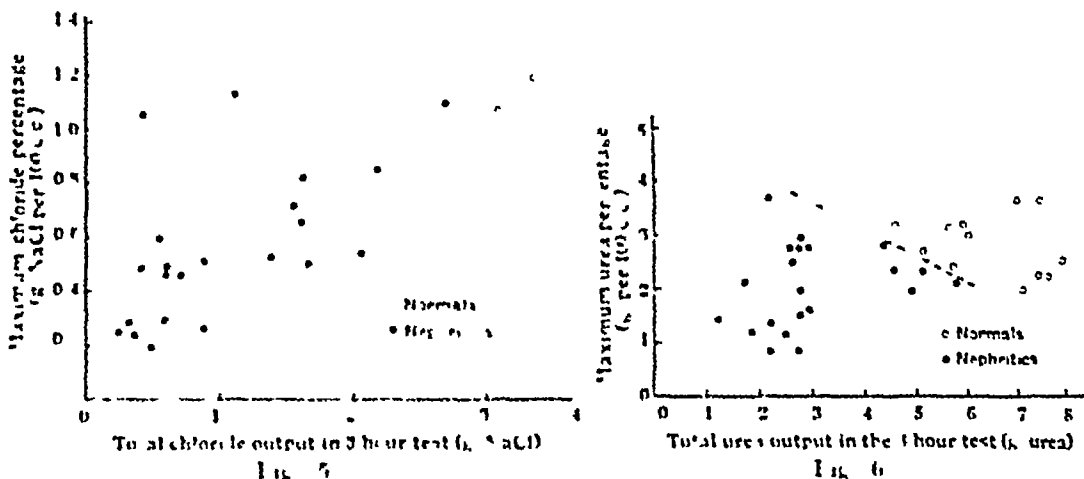


Fig. 5. The maximum chloride percentage and the total chloride excretion in normal and nephritic subjects following the administration of 17 grams of urea and 4 grams of potassium chloride

Fig. 6. The maximum urea percentage and the total urea excretion in normal and nephritic subjects following the administration of 17 grams of urea and 4 grams of potassium chloride

It is, therefore, evident that under similar experimental conditions practically all patients with nephritis can be distinguished from normal subjects either by their urea or by their chloride excretions. In addition the results provide confirmation of the conclusion reached in Section 1 that the inability of patients with Bright's disease to produce percentages of sodium chloride above 0.8 in the urine under these conditions is not due to a slight and unrecognised deficiency of salt

The value of the expression $C + \frac{U}{2}$ (U = the maximum urea % and C = the NaCl concentration in the urine sample where the maximum urea concentration was obtained, both concentrations being expressed in g per 100 cc) effects a similar separation between normals and patients with nephritis to that described in Section 3b and illustrated in Fig 4. The result of one normal test is discounted because of the unusually large diuresis. Again the best separation between normals and patients with nephritis has been effected by the use of $C + \frac{U}{2}$. But where chloride is given in addition to urea there are 3/20 nephritic cases where the value of $C + \frac{U}{2}$ is over 2. A value of 2 or more was only obtained, however, in very mild cases. It is to be expected that the damage to renal function in mild focal

nephritis may occasionally be so slight as to cause no change which can be detected by biochemical tests

From these results it would appear that this form of test supplies most of the information to be gained by the test described in Section 1, which requires the analysis of a larger number of urine samples. In a small number of cases, however, the diuretic action of the potassium has been so great that the urea concentration has only just attained 2% and in 2 instances has been just below 2%. Thus, however, does not give rise to any difficulty in deciding whether the renal function is normal or abnormal provided the urine volumes are taken into account. When the rate of urine formation is no greater than 100 c c per hour a urea percentage of 2 should be attained by all normal subjects.

The modified test appears, therefore, to be almost as satisfactory as the first test described in which urea alone is administered and is very easily carried out with even less trouble to the patient than the routine adopted for the urea concentration test.

The first test using urea alone is rather more sensitive to slight renal damage, this test using urea and chloride is less liable to give a slightly abnormal response on a normal subject.

As the urea and chloride normally account for most of the solids in the urine, the maximum specific gravity of the urine attained a few hours after giving urea will be a rough indication of the presence or absence of renal disease.

The specific gravity is much more closely related to the quantity $C + \frac{U}{2}$ than would be supposed at first, for the specific gravity does not merely depend upon the concentration but upon the nature of the dissolved constituents.

The following figures are given by *Albarran* (1905) (1). At 15°C an increase in the specific gravity of 0.001 is caused by the addition to 1 litre of urine of

1.473 g of sodium chloride
3.595 g of urea
2.700 g of glucose
3.892 g of albumen

In its effect upon the specific gravity, the total osmotic pressure and the freezing point depression of urine, salt is about twice as potent as urea, so that any of these should be an approximate index of changes in $C + \frac{U}{2}$.

The presence of other physiological constituents, and of pathological constituents such as albumen and glucose, may make the changes in the specific gravity of urine after giving urea (or urea and chloride) less reliable as an index of slight grades of renal damage. In order to make use of the specific gravity at all it is of course necessary to use accurate hydrometers and to correct for the temperature of the urine.

Section 5 Urea and chloride excretion in early renal lesions in diseases other than simple nephritis

In Sections 1 to 4 it has been shown that in diffuse nephritis, however mild, a defect in the manner of excreting urea or chloride can be demonstrated by the tests described. It would be of great practical value if such a test could be used as an indication of very slight and early renal damage in the course of other diseases when their complication by nephritis may be expected. For this reason cases of hypertension, infective endocarditis, slight prostatic obstruction, and diabetes mellitus with albuminuria etc., were studied in the hope of finding some abnormalities in the urea and chloride excretion

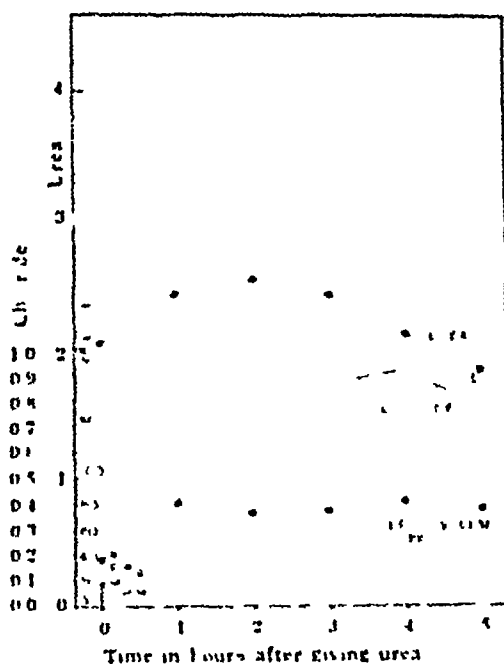


Fig. 7. Observation A1 Normal

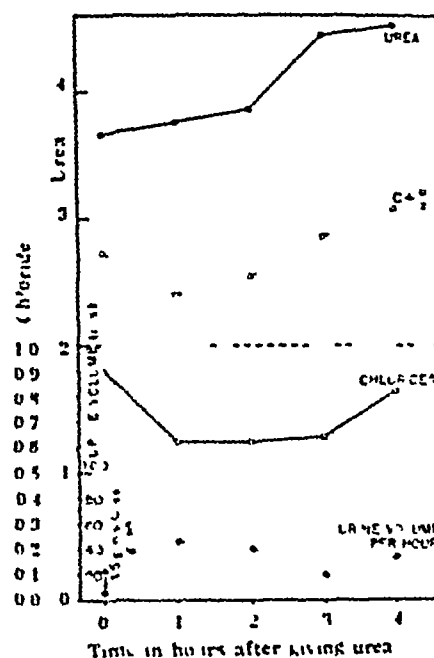


Fig. 8. Observation A20 Normal

Fig. 7-12 The effect of urea administration upon the percentages of urea and chloride in the urine and the rate of urine formation. The values of $C + U$ may be read on the scale for urea percentages.

which might be the result of early renal disorder. The results to be quoted in brief comprise 10 tests on 36 patients. They suggest that the abnormalities in the excretion of chloride which often make their appearance before other evidence of renal damage is found, do in fact, indicate early renal lesions. But although the evidence so far points in this direction the results are to be regarded as preliminary and requiring further investigation except in regard to the one point which concerns this paper.

(a) *Cases of arterial hypertension* Six cases with hypertension and 2 cases with hypertension and heart failure with congestion have been studied. Six of the cases received 15 g. of urea, and 2 cases were given the urea and chloride mixture. In the cases without heart failure hypertension was

discovered in the course of a routine examination and the patients were without symptoms referable to the raised blood pressure. The systolic blood pressure was above 170 mm of mercury in all cases, but as judged by the urea concentration test, their renal function was good, Case B 5 being only an apparent exception because the relatively low urinary urea concentration was the result of a large diuresis.

In 4/6 hypertensive cases the chloride concentration was well below the usual normal level and in only one test was the renal function clearly normal as judged by this test. In the 2 cases of hypertension with heart failure of the congestive type, the chloride concentration was also low. It must be emphasised at this stage that heart failure with congestion may also reduce the urinary output and may reduce the chloride percentage in the urine. In the author's view, the functional derangement of the kidney resulting from heart failure with congestion is often as great as in many cases of nephritis. In 5/8 cases the value of the expression $C + \frac{U}{2}$ was less than the minimum normal value of 2.

(b) *Cases of infective endocarditis* Eight cases of infective endocarditis have been studied. One of them developed clinical nephritis with oedema while under observation. The remaining 7 are described below.

3/7 of these, while showing no clinical evidence of nephritis had urinary urea concentrations of 1.15, 1.75, and 1.0% and the chloride excretion in all was defective. The urea was well concentrated in the remaining 4 but in 2 of these the expression $C + \frac{U}{2}$ was below 2, it was within normal limits (just over 2) in the remaining 2 cases.

Caution must be exercised in interpreting defects in the chloride excretion as evidence of defective renal function in cases of infective endocarditis because the percentage urinary chloride and rate of chloride excretion are known to be diminished in cases where the body temperature has recently been above normal. This is illustrated in the following cases —

(c) *After the crisis in pneumonia* Only two cases were investigated. Both of these had a trace of albumen and casts in the urine for several days after the temperature had returned to normal. In two successive tests on S the chloride concentrations were 0.64 and 0.79. The expression $C + \frac{U}{2}$ was above 2 in both cases. M, however, had many more casts in the urine and the urinary chlorides were 0.04, 0.46, and 0.86% in 3 successive tests although the expression $C + \frac{U}{2}$ was normal. It is usually supposed that the urinary chloride in pneumonia is low because the plasma chloride is subnormal. But in this case the plasma chloride was raised at the time when the urinary chloride was low and it decreased during the next few days as the urinary chloride was increasing. The value of the plasma chloride was 0.656 at the time that the urinary chloride was 0.04. This increase in plasma chloride was not the result of a diminution in the plasma protein (see Section 1 (d)) as this was normal. The chemical determinations were confirmed with particular care and there was no question of methodical

error Such a result suggests that the chloride retention in pneumonia may result sometimes from renal as well as from extra-renal causes

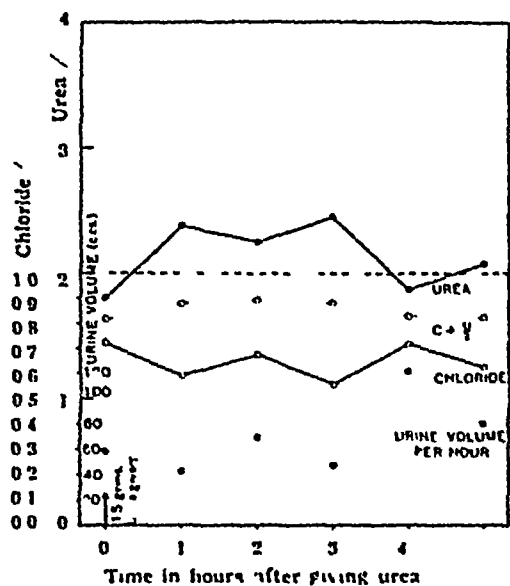


Fig 9

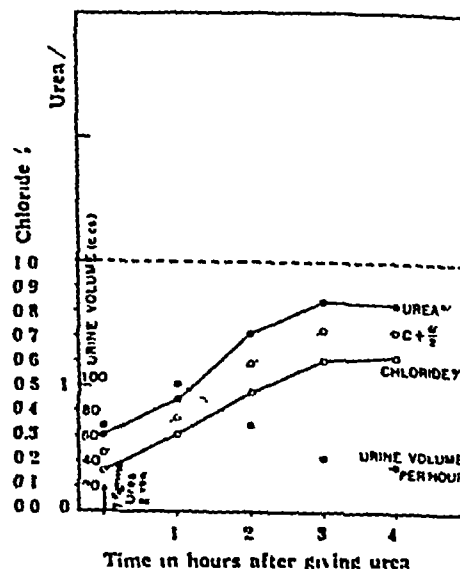


Fig 10

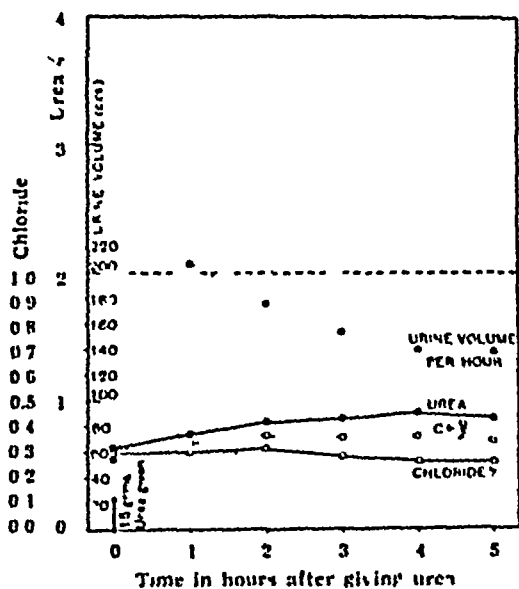


Fig 11

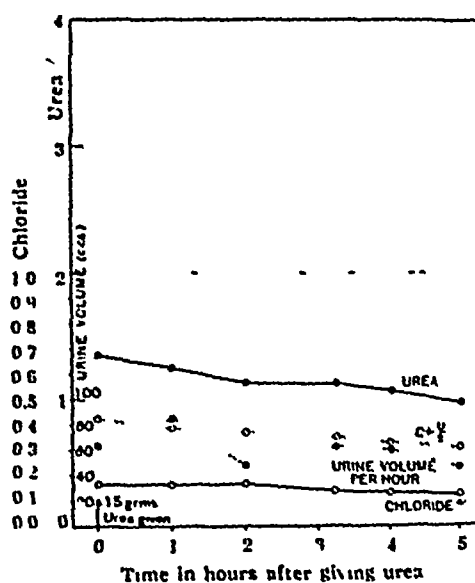


Fig 12

- Fig 9 Observation C 11 Nephritic (mild), perfectly well $7\frac{1}{2}$ years after the test
 Fig 10 Observation C 62 Nephritic (mild), moderately well $4\frac{1}{2}$ years after the test
 Fig 11 Observation C 65 Nephritic (severe "compensated"), very well $7\frac{1}{2}$ years after the test
 Fig 12 Observation C 3 Nephritic (severe "uncompensated"), died a few weeks after the test

(d) *Cases of pernicious anæmia* Three cases were studied. The results were in all respects normal. In the two cases where it was tested, the urine was quite free from albumen.

(e) *Cases of diabetes mellitus with slight albuminuria* Five cases were studied. Two patients were passing no sugar in the urine and gave results which were quite normal. Three cases were passing between 2 and 3% sugar in all samples. In these cases the chloride concentration was low and the expression $C + \frac{U}{2}$ was under 2. The plasma chloride and blood sugar were estimated and it was found that in any single case there was an inverse relationship between them. It seemed as though the osmotic pressure of the blood was maintained at its normal value by a temporary diminution in the plasma chloride compensating for the hyperglycæmia. This fall in the plasma chloride may explain the low urinary chloride. Alternatively it may be that the kidneys reduce the osmotic resistance of the secreted urine by passing out less chloride whenever the additional work of concentrating sugar is to be performed.

(f) *Cases of mild prostatic obstruction* Three cases were studied. The urea concentration was above 2% in all, but the expression $C + \frac{U}{2}$ was below 2 in one case and at the lowest limit of normal in the remaining 2.

(g) *Cases of albuminuria but no other evidence of any renal lesion* Four cases were taken, all well past the years of adolescence. All cases had urea concentrations of over 2%. The blood pressure in all was normal, and 3/4 tests showed no functional abnormality. In the remaining case the chloride concentration was low and the expression $C + \frac{U}{2}$ was below 2.

(h) *Cases with various renal conditions likely to influence the renal function* In a case of unilateral renal calculus the function of the kidneys as inferred from the results of the test was normal. In a case of hydronephrosis the expression $C + \frac{U}{2}$ was under 2. In A. H. the case referred to in Section 2 (b), the urinary urea concentrations were 1.5 and 1.1 and the chloride concentrations were 0.37 and 0.81 in successive tests. The renal function was excellently maintained by means of a large compensatory diuresis. The diagnosis was not certain, but most probably there was present a congenital cystic condition of the kidneys.

From Sections 3 and 4 it does not appear to matter whether the value of $C + \frac{U}{2}$ is determined in tests where urea is given alone or in combination with chloride. In each case with few exceptions the normal value is 2 or more, the abnormal under 2.

Summary of Section 1

1 The effect of giving 15 g. of urea by mouth upon the urinary chlorides, has been investigated in normal subjects and patients with nephritis.

2 Most normal subjects under stated conditions attain a urinary chloride of 0.8 (as NaCl), or more, either in the early morning sample passed

before taking urea, or during the 4 or 5 hours after urea administration. Under similar dietetic conditions the urine of patients with nephritis rarely attains a chloride percentage of 0.8.

3 Both in normal subjects and patients with nephritis the administration of 15 g of urea increases for a few hours the rate of chloride excretion. In general, greater increases are obtained in normals than in patients with nephritis even when they start with the same rates of chloride excretion before urea is given.

4 Similarly, greater increases in the percentage of urinary chloride are obtained in normals than in patients with nephritis even when they start with the same chloride percentage before urea is given.

5 Both in normals and in patients with nephritis the plasma chloride is only slightly changed by giving 15 g of urea in 100 c.c. of water, and whereas the plasma chloride tends if anything to fall, the percentage urinary chloride and the rate of chloride excretion is generally raised. For equal percentages of the plasma chloride the normal subjects have as a rule higher urinary chloride percentages than have patients with nephritis.

6 From these observations it is concluded that the increased chloride excretion after giving urea is not caused by the mobilisation of extra chloride into the blood. Also that the relatively small chloride excretion in nephritis without oedema is not the result of a diminution in the plasma chloride below the normal value, and most probably is of renal not extra-renal origin.

Summary of Section 2

1 The maximum urea percentage in the urine is most commonly encountered in the 4th or 5th hour after giving urea, and many patients with nephritis do not attain a percentage of 2 until the 4th or 5th hour. The time relations of the ordinary clinical urea concentration tests are, therefore, important.

2 In nephritis patients with a maximum urinary urea concentration of over 2% it is of interest to note that only in 8 out of 26 cases does the urine attain a urea concentration of 2.5 or more whereas in normal subjects a percentage of 2.5 was attained in 29 out of 32 tests. Again in these patients a urinary chloride concentration of 0.8 or more is attained in only 2 out of 24 as contrasted with 22 out of 33 in normal subjects.

3 In nephritis patients as contrasted with normal subjects a high urea percentage is usually attained at the expense of the urinary output and if the maximum urea percentages and the corresponding rates of urine formation are considered together a much more complete separation between mild cases of nephritis and normal subjects may be made, than by using only the urea percentage.

4 The total amount of urea excreted in the 4 or 5 hours after giving urea is of value in that it indicates whether urea retention would be likely to occur with much protein in the diet

5 Fixation of the urea percentage at a low level (say 0.9 to 1.2) is usually but not always an indication of bad prognosis. A case is quoted where a patient had a fixed urea percentage of about 1 for 7 years, felt well, even played football, and shows no signs of progressing damage

Summary of Section 3

1 During the 4 or 5 hours following the administration of 15 g of urea in 100 c.c. of water it is observed that in patients with nephritis the rises in the urinary urea percentage are frequently accompanied by falls in the chloride percentage. Similarly when the urea percentage falls the chloride percentage tends to increase. In these patients it is rare for high concentrations of urea and chloride to be attained in the same urine sample

2 In normal individuals this inverse relationship between the urea and chloride percentages is uncommon, and high concentrations of urea and chloride are often encountered together

3 If in tests on normal subjects and patients with nephritis we select the urine samples in which the maximum urea percentages are attained, and then compare, in the two groups, those urine samples with the same urea percentages, it will be found that the chloride percentages attained in those samples are almost invariably less in nephritis than in health

4 If U = the maximum urea % in a 4 or 5 hour test C = the chloride % (as NaCl) in the urine sample where this concentration was obtained, then the expression $C + \frac{U}{2}$ is greater than 2 in practically all normal subjects provided that the diet has not been very poor in chloride, and less than 2 in practically all cases of nephritis, however mild

5 A diet very poor in chlorides will reduce the maximum chloride percentage, however, and may even reduce the value of $C + \frac{U}{2}$ to below 2

6 In patients with severe nephritis and inability to concentrate urea the chloride percentage in the urine is at all times less than that in the blood. Although the urea percentage in the urine is greater than that in plasma the urinary chloride is so much below the plasma chloride that the osmotic pressure of the urine due to urea and chloride is about the same as the osmotic pressure of the plasma due to these two substances. It is probable that the low chloride concentration allows urea to be concentrated with less difficulty

Summary of Section 4

1 The effect upon the urine composition of giving 13 g of urea and 3 g of potassium chloride by mouth to normal subjects and patients with nephritis has formed the basis of a practical test of renal function

2 Most normal subjects under these conditions attain a urinary urea percentage of 2 or more and a chloride percentage of 0.8 (as NaCl) whereas most patients with nephritis fail to attain a chloride percentage of 0.8

3 The observations made in items 3 and 4 of the summary of Section 3 apply equally to this investigation

4 The total urea excretion during the 3 hour test is less in patients with nephritis than in normal subjects with the same maximum urea concentration. It appears, therefore, that in nephritis a urea concentration of 2% or more is usually attained at the expense of the urine output

Summary of Section 5

1 The tests described in Sections 1 to 4 have been applied to cases of (a) arterial hypertension, (b) infective endocarditis, (c) pneumonia after the crisis, (d) pernicious anemia, (e) diabetes mellitus with albuminuria, (f) mild prostatic obstruction, (g) albuminuria without other evidence of a renal lesion, and (h) various conditions likely to influence renal function

2 It has been shown that in many of these patients a functional abnormality is revealed by the application of the above tests

3 This is taken to indicate that the chloride excretory function of the kidneys is modified by very slight renal defects and by damage even of a temporary nature

GENERAL SUMMARY

1 A study has been made of the excretion of urea and chloride in the urine of healthy subjects and of patients with diffuse renal disease. Based upon these observations are described two sensitive tests of renal function which depend on the analysis of urine samples only

2 A hypothesis involving the diffusion of water from blood through the walls of damaged tubules has been suggested, and this appears to explain the composition of the urine in cases of advanced chronic nephritis

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BLOOD-PRESSURE OBSERVATIONS WITH A NEW TYPE OF OSCILLOMETER

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A REASON for adding another to the multitude of existing apparatus for determining the blood-pressure by oscillographic methods is that in the instrument here described the sensitivity can be increased almost indefinitely. Furthermore, readings can be taken (1) from any point of the body to which a pneumatic cuff can be applied, (2) with a rapidity very little less than that of the auscultatory method, and (3) with much greater certainty than by auscultation. On the other hand, no permanent record is obtained, but this is largely compensated by the rapidity with which readings can be made. The instrument is an application of the principle of Whiddington's ultramicrophone (15), a principle remarkably little employed in physiological apparatus, to the measurement of the amplitude of the oscillations transmitted from the air-cuff.

Description of apparatus

(a) *Electrical* A and B (Fig. 1) are two oscillating valve circuits coupled together at X. A, in addition to being an oscillator, is arranged for leaky grid rectification and has a loud speaker connected either directly in its anode lead or through a single stage of low frequency amplification. The frequency of the oscillators can be altered within limits by the variable condensers L and M. The frequency of circuit B is also controlled by a special condenser N (to be described later), in which the capacity varies with the magnitude of the air pulses transmitted from the sphygmomanometer armlet.

When the two circuits are in resonance, no sound is heard from the loud speaker, over a small range on either side of the resonant point, an audible beat note is produced which rises in pitch to inaudibility as the separation of the frequency of the two circuits increases.

In use the condensers L and M are so set that the beat note is high pitched with N at rest, and is lowered in pitch by the air pulses received at each pulse beat. The greater the amplitude of movement of the arterial wall, the greater the capacity change at N and the lower the note reached. The systolic pressure is signalled by the slight glissando at each pulse (due to the impact of blood on the upper edge of the armlet) becoming suddenly greater in range, and the diastolic by the point at which, after the maximum range of pitch variation has been reached, the lowest note of the glissando begins to rise. In short, the graphic oscillations of an Erlanger blood-pressure oscillograph are rendered as variations in pitch.

If N is made comparatively insensitive, the whole range of pitch variation between systolic and diastolic points can be accommodated without altering the settings of L and M. Much more critical readings can be obtained, however, by having N sensitive and, after the systolic point has been passed, 'following up' the changes by manual rotation of L so as just to keep the circuits out of resonance until the diastolic point is approached, when condenser L is left set. After very little practice, this becomes an easy operation and the reading can readily be repeated in case of doubt. This electrical part of the apparatus is enclosed within a metal lined earthed box to prevent radiation.

(b) *Construction of condenser N* A short length of brass tube A (Fig 2) is inserted through a rubber bung, and one end compressed to elliptical shape. Across the major axis of the ellipse is fixed a flat piece of ebonite, B, shaped to a suitable curve at its upper end, and of insufficient thickness to fill completely the elliptical opening. Over the ebonite from above downwards is rolled an indiarubber finger stall, C, its open end fitting snugly over the outer surface of the elliptical end of the brass tube. A U shaped piece of very thin tinfoil is then fixed to the outer surface of the stall with rubber solution so that the two limbs of the U lie, one on each side of the flattened stall and the base of the U partly encircles the portion of the stall on the brass tube. A fine insulated wire connection having been soldered to a small piece of thin copper foil, this foil is laid on the base of the U of the tinfoil, and a narrow width of insulating tape wound tightly around the base of the stall where it fits the brass. In this way, a satisfactory electrical connection to the tinfoil and an airtight junction between brass tube and stall are simultaneously secured. The other end of the connecting wire is soldered to a stouter wire which passes air tight through the bung.

The second electrode of the condenser is formed by two moderately rigid metal plates, D, fixed to the brass tube at their lower ends and having at their upper ends holes through which passes a small bolt and nut. The inner surfaces of the two plates are covered with waxed paper and by adjusting the bolt and nut, the plates can be brought into very close approximation to the tinfoil lined finger stall. Electrical connection to these plates is conveniently obtained by a wire soldered to the lower end of the brass tube.

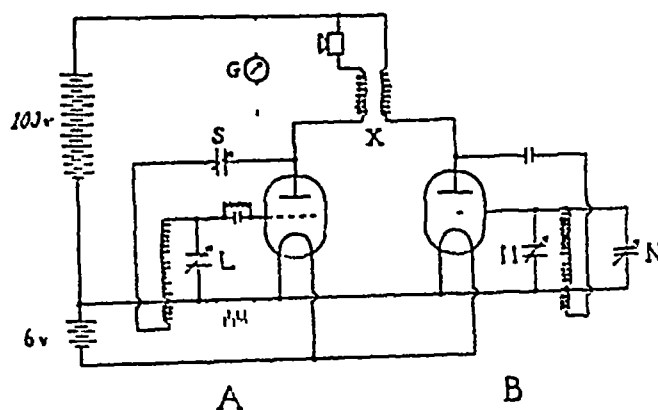


Fig 1

The whole assembly, by means of the rubber bung, is fixed into a glass chamber tapering at the top to a narrow tube. Through a rubber stopper fitting tightly into the lower end of the brass tube passes a glass tube which connects (1) through a capillary EF with the tube at the upper end of the chamber, (2) again through a capillary (to damp oscillations) with a mercury manometer, and (3) with the anode.

The arrangement as so far described constitutes an oscilloscope of the Pachon type in which slow changes of pressure in the system are equalised on the two sides of the finger stall membrane but rapid fluctuations of pressure such as those caused by the pulse waves are transmitted mainly to the inside of the finger stall owing to the interposition of the capillary between chamber and anode tube.

(c) *Inflation and leak system* With so sensitive an oscilloscope, the leak by which the pressure in the system, after being raised above systolic is allowed to diminish must be a very steady one. Any sudden fluctuations in the leak, even though small, cause adventitious changes in the pitch of the beat note which are very confusing.

A much more troublesome difficulty is to arrange that the pressure shall diminish by equal amounts in equal times. With the ordinary minute aperture the pressure falls exponentially

By adopting the dotted line parts of the circuit (Fig 1) in place of the corresponding full line portions, and by diminishing the capacity of the semivariable condenser S until A is just short of oscillation, a visual indication of the amplitude of the pulse changes may be obtained in the range of the "fluctuations" of the needle of a sensitive milliammeter G. B is then acting as a small transmitter and A as an anode bend detector. The induction given on the meter is similar to that of the Pachon oscilloscope. In the author's opinion, the auditory arrangement is preferable and all the data here recorded have been so obtained.

and the slight differential pressure which, owing to the constriction between the air spaces connected with the inside and outside of the rubber membrane, must exist between them, is relatively large at high pressures and relatively low at low pressures. There would thus be a slight change in the position of the membrane relative to the plates, as the pressure fell from above systolic to zero, and, as a result, the pitch of the beat note would drift during the observation. It is absolutely essential to eliminate this drift, otherwise erroneous readings will be obtained.

For this purpose, a combination of two methods was adopted. First, the capillary constriction between the exterior and interior of the rubber membrane is divided into two portions, E and F, and the leak is taken from a point between them. The lengths of E and F are then adjusted so that the "pull" of the leaking air is exerted equally on the external and internal surfaces of the membrane. Secondly, the leaking air is allowed to escape through a mercury column whose height varies with the pressure in the whole system. The arrangement is shown in the right hand portion of Fig. 2.

A T junction from a point between capillaries E and F leads (1) to the inflating bulb, G, thence (2) to a bottle H, acting as an air reservoir, and (3) to a second bottle, J. J is partially filled with mercury and, in addition to the air-entry tube, has a wide bore glass tube, K, at least 300 mm long, extending almost to the bottom of the bottle. The air-exit for reservoir H is led

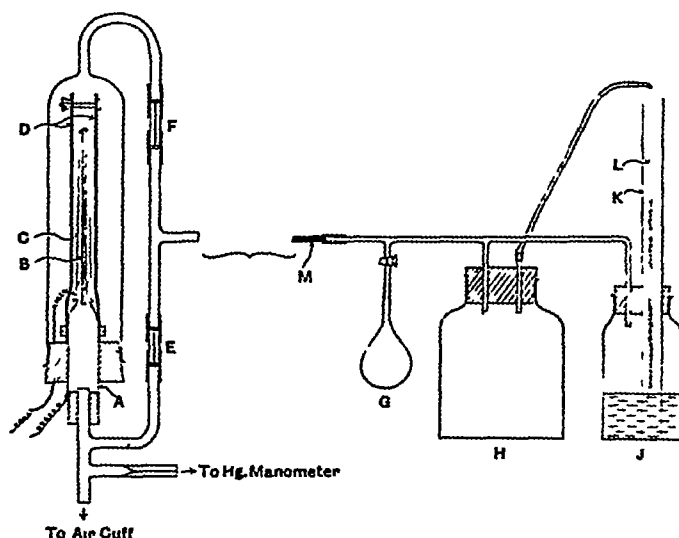


Fig. 2

by rubber tubing to a narrow glass tube L, which extends down into the tube K to a point a few millimetres above the mercury surface at zero pressure. When the pressure in the system is raised, the pressure causing air to leak through L is equal to the pressure in the system less the height of the mercury column in K above the exit of L. Since the mercury column in K falls with the fall in pressure in the whole system, the leak pressure remains constant until the mercury descends below the exit of L. Capillary M and reservoir H damp oscillations produced by the bubbling of the air through the mercury in K.

With this arrangement, drift of the beat note can be avoided down to a pressure of 20 mm or a little less. The efficient working of the arrangement, and the absence of adventitious leaks in the system, are tested for from time to time by fixing the armlet on a rigid cylinder of convenient diameter, inflating to 250 mm, and observing the constancy of the beat note as the pressure falls to zero.

EXPERIMENTAL OBSERVATIONS

Since the special features of the oscillogometer are its sensitivity and its adaptability to any region of the body where a pneumatic cuff may be attached, observations were made on the following points —(1) the relation of the systolic and diastolic pressures as given by the present oscillogometer

to those obtained by the auscultatory method, (2) the relation of the pressures obtained at different levels above and below the heart to hydrostatic pressure, and (3) the pressures in the smaller arteries for which an ordinary oscilometer is insufficiently sensitive

Five subjects of widely different age were used —A, male, 27 yrs, B, male, 37 yrs, C, female, 38 yrs, D, female, 60 yrs, and E, female child, 6 yrs. All were in good health

The procedure is as follows. A broad rubber cuff, long enough to completely encircle the arm, and surrounded by an unyielding cover of webbing provided with straps and buckles, is used as armlet. After this is adjusted and connected to the oscilometer, condenser M is set at minimum, and condenser L rotated until a high-pitched beat-note is heard in the loud-speaker. Inflation is then carried out to a point about 30 mm above the systolic pressure in order to give time for the pressures throughout the system to stabilise and for the automatic leak to become regular. During this period L is readjusted if necessary so that the slight oscillations caused by the impact of the blood on the upper border of the cuff just audibly depress the high pitch of the note.

As the systolic pressure is passed, there is a rapid and progressive lowering of the note at each pulse-beat. The highest pressure at which this progressive lowering of the note is detected is recorded as the systolic pressure. With further fall of pressure, the glissandi of pitch increase in range and, if L is left untouched, the oscillating circuits will, at each pulse, pass through resonance and a second change in pitch, which rises with increasing amplitude, will succeed the falling one. This double change is confusing and is avoided by altering L, after the systolic reading has been made, so as to keep the circuits just short of resonance.

The approach of the diastolic level is heralded by the range of the pitch variation becoming constant, at this point L is left set and the first rise in the lowest note reached at each pulse carefully listened for. This rise, which is very sharply marked—much more so than the systolic—is taken as the diastolic index.

The results reported in all the following tables are the averages of a number of consecutive observations in each case. Except in a few instances, where greater accuracy was desirable, averages are given to the nearest mm Hg.

A *Relation of results to usual systolic and diastolic criteria*

In adopting the above method, the criterion for systolic pressure is the beginning of the marked progressive increase in the oscillations, and the diastolic criterion the point at which oscillations, having become maximal, first begin to diminish. With the original comparatively insensitive oscillographs, the first appearance of any oscillations was taken as the systolic index. As the sensitivity of apparatus was improved sufficiently to record the oscillations produced by the impact of blood on the armlet

before penetration, the accepted criterion became the point at which these impact oscillations increased in magnitude Erlanger (5), suggested that, as this increase was frequently not at all sudden, a better index was the broadening of the base of the wave recorded on the oscillograph, a broadening due to the longer time necessary for the armlet and recording system to recover when blood, which had penetrated, had to be squeezed out from below the cuff, than when the recording system had to recover merely from the shock of impact It is generally accepted that this phenomenon is synchronous with the first appearance of Korotkow sounds In a later paper Erlanger (6) stated, however, that "under all circumstances a sudden increase or decrease of amplitude, if present, indicates accurately the systolic and diastolic pressures" This sudden increase we have rarely failed to obtain during any observation and, where it has failed, a single repetition of the observation has sufficed to give a readable index

A comparison with the Korotkow sounds shows that this index of marked amplitude increase, as detected by the present oscillograph, gives slightly higher results (average + 4 mm) than the auscultatory method, (Table I)

TABLE I.

Subject	Aver syst press		Differences
	Oscill	Auscult	
A	109.5	105	+ 4.5
C	127.3	124	+ 3.3
	127	124.7	+ 2.3
D	114	108	+ 6.0
	122	118.7	+ 3.3
			Aver + 3.9

Systolic pressures as so recorded, though higher than those obtained by auscultation, are undoubtedly closer approximations to the true intra-arterial systolic pressure Penetration through the cuff of the pulse-wave, as Erlanger (7) showed, is a relatively gradual occurrence, taking place over a range of several millimetres of falling external pressure The true systolic pressure must lie in the zone of the partial penetrations since such partial penetrations must, to some extent, inhibit their own passage by momentarily raising the cuff pressure above the value existing when the wave enters the cuff Because of the gradual penetration, Erlanger (7) estimates that any index, such as the auscultatory one or the broadening wave base, which depends on complete penetration, must give results at least 8 mm Hg too low, and, in the same publication, he favours in theory the index of suddenly increasing amplitude, though its frequent lack of definition in the usual oscillographic tracing has made it of little practical value

Certain observations on the peripheral palpation index of systolic pressure may be referred to here. It is generally accepted that the palpation of the pulse peripheral to the cuff yields lower results for the systolic pressure than the auscultatory method, comparisons show a difference of 5 to 15 mm in favour of the latter. A few experiments with subject A were carried out in which the brachial systolic determined by auscultation was compared with the results obtained when the first radial pulsation, detectable by our oscilometer in its most sensitive condition, was used as index. This comparison gave, on average, a systolic pressure actually higher by 2.3 mm than the auscultatory method. It is thus possible, given a sufficiently sensitive recorder, to show that the pulse-wave does penetrate the cuff at, or slightly above, the appearance of the first sound. This lends further support to the view that the oscillographic criterion adopted above of the first marked rise in amplitude, which, in the same subject is 2.2 mm higher still, is a slightly nearer approach to the true systolic pressure than either the first sound or the criterion of the broadening wave-base.

The diastolic criterion which must necessarily be adopted with the present apparatus is that of the beginning of abrupt diminution in amplitude. It is now generally accepted that the true diastolic pressure falls within this diminution zone rather than at the maximal oscillation point, though some difference of opinion exists as to precisely which point in the diminution zone is the correct index. McWilliam and Melvin's (12) criterion is the point "just after" abrupt diminution in amplitude has occurred while Erlanger (7) would place the diastolic at a somewhat higher pressure "where the accelerating decrease in amplitude changes to a retarding decrease". Our diastolic index might be very slightly higher than even Erlanger's, on the other hand, we have found good agreement between our criterion and the fourth phase of the Korotkow sounds, which is now very generally accepted as a reliable indication of the diastolic pressure (Table II).

TABLE II

Subject	Aver diast press		Difference
	Oscill	Auscult	
A	70.5	72	- 1.5
C	84	85.5	- 1.5
	83	80	+ 3.0
D	72	73	- 1.0
	77.3	76	+ 1.3
			Aver + 0.06

The method of determining the diastolic pressure by the amplitude of oscillation peripheral to the cuff was investigated. The oscilometer armlet was placed around the wrist and inflated just sufficiently to record. A

second cuff connected to a manometer was then placed around the arm and slowly inflated until the first diminution of the size of the radial pulse was heard. While such results as were obtained did not conform to the experience of others in giving unduly high diastolic values, the changes were poorly marked and the method was not pursued.

B *Systolic and diastolic pressures in relation to level and posture*

L. Hill and co-workers (10) investigated the systolic blood-pressure at different parts of the body in different postures and found that, in the horizontal position, the pressures were identical in arm and leg in normal subjects, but that in subjects with arteriosclerosis the leg pressures were higher, a fact which they attributed to the better conduction of the systolic wave by the more rigid arteriosclerotic vessel. In normal subjects placed in postures other than horizontal, the systolic pressure taken at any two points differed exactly by the hydrostatic pressure of the column of blood between them. No observations of diastolic pressure were made by Hill and his associates, but it might very reasonably be expected that the diastolic pressures at different points above and below heart level would depend even more rigorously on the effect of gravity.

Now it is quite possible for a six-foot man to assume an L-position, with thighs and legs flexed at right angles to the body, in which the foot is

TABLE III

Subject	Aver syst		Aver diast		Differences	
	Arm	Ankle	Arm	Ankle	Syst	Diast
A	106	109	65	68	+ 3	- 3
	110	114	67	68	+ 4	- 1
	107	113	66	65	- 6	- 1
	102	106	65	64	+ 4	- 1
	108	116	72	70	- 8	- 2
	110	117	74	74	- 7	0
	122	127	65	67	+ 5	- 1
					Av - 5.3	- 0.1
C	133	138	92	92	- 5	0
	121	128	80	82	- 7	+ 2
					Av - 6	- 1
D	119	137	71	73	+ 18	- 2
					Av + 18	+ 2
I	100	105	62	61	+ 5	- 1
	109	115	70	71	- 6	- 1
					Av - 5.5	0

45 inches above the level of the brachial artery. The systolic pressure in the brachial artery under such conditions remains, as Hill showed, practically unaltered. If brachial systolic and diastolic are assumed to be 120 mm and 80 mm, then, according to Hill's contention, the corresponding pressures in the arteries of the foot must be approximately 30 mm and -10 mm. Such pressures seem inconceivable, especially in view of Carrier and Rehberg's (2) findings, confirmed by Landis (11), that the capillary pressure is constant at a small positive pressure, at any point higher than 7 cm below the clavicle. Moreover, the appearance of the foot gives no suggestion of such a state of affairs.

The existence of a differential systolic pressure in arm and leg in the horizontal posture was re-investigated by Burdick *et alia* (1). They argued

TABLE IV

Subject	Aver syst		Aver diast		Relation of ankle to brach + hydr press	
	Arm	Ankle	Arm	Ankle	Syst	Diast
A	113	202	76	165	- 9	+ 9
	115	196	79	157	- 2	- 1
	117	191	75	154	- 3	+ 6
	112	191	79	155	0	- 3
	115	194	82	155	+ 2	- 4
	113	203	79	168	+10	+ 9
					Av + 3.3	- 2.7
C	127	217	91	183	+ 2	+ 4
	125	220	93	184	+ 4	+ 3
					Av + 3	+ 3.5
D	133	204	79	160	- 5	+ 5
	122	199	72	163	- 2	+12
					Av - 3.5	+ 8.5
F	102	151	64	116	- 2	+ 1
	112	154	78	123	- 3	0
					Av - 2.5	+ 0.5

that, if a difference was evident in subjects with arteriosclerosis by the comparatively insensitive method used by Hill, a certain difference might be found in normal subjects if modern sensitive methods of recording were employed. Such differences were found but they varied widely from 27 to 60 mm Hg.

A re-investigation of these points with the present oscillometer gave interesting results. Table III shows the systolic and diastolic pressures

taken from the arm and the ankle, when the subject was lying on a bed with these parts on exactly the same level. In these experiments two cuffs were used, one in the usual position over the brachial, and the other encircling the leg just above the ankle-joint. Readings were taken from each cuff alternately.

It will be seen that the leg systolic is consistently higher than that of the arm, while there is no significant difference in the diastolic. The systolic differences are, however, much smaller than those found by Burdick and others (1). A point of interest is that the largest difference was found in the oldest subject though the absolute values of the systolic gave no indication of any arterial hardening. On the other hand, the difference found in the younger adults was also found in the child of six, in whom presumably arterial elasticity was best of all.

Table IV shows the differences in systolic and diastolic pressures recorded from arm and ankle when the subject was in the standing position.

TABLE V

Subject	Hydr press	Aver syst		Aver diast		Excess of ankle over brach less hydr press	
		Arm	Ankle	Arm	Ankle	Syst	Diast
A	48	104	82	65	27	+ 26	+ 10
	48	105	83	69	34	+ 26	+ 13
	48	105	86	66	33	+ 29	+ 15
	47	105	86	66	33	+ 28	+ 14
	46	107	87	66	27	+ 26	+ 7
	45	105	93	67	31	+ 33	+ 9
	44	110	93	66	27	+ 27	+ 5
	42	111	95	71	30	+ 26	+ 1
	39	98	76	67	37	+ 17	+ 9
	34	112	94	73	47	+ 16	+ 8
	33	101	89	66	41	+ 21	+ 8
	31	114	95	70	47	+ 12	+ 8
	30	102	89	66	41	+ 17	+ 5
	28	120	105	67	43	+ 13	+ 4
C	56	122	86	80	47	+ 20	+ 23
	30	137	117	94	66	+ 10	+ 2
	18	122	104	80	64	0	+ 2
D	45	125	98	71	37	+ 18	+ 11
	24	125	110	71	52	+ 9	+ 5
	22	119	104	68	52	+ 7	+ 6
E	22	100	85	63	43	+ 7	+ 2
	16	108	92	72	56	0	0

The figures here undoubtedly support the contention of Hill that the difference in pressure between two points is that which would be expected from the hydrostatic pressure of the blood between them. This is true of both systolic and diastolic. There is, however, this reservation. The slight differential pressure between arm and leg, found in the horizontal position, is not evident in these figures. Whether this indicates a real

absence of this differential pressure or not is doubtful. The differential pressure is small and an error of 1.3 cm in the measurement of the blood column between the cuffs would account for a pressure difference of 1 mm Hg. This measurement cannot be accurate because, quite apart from slight movements of the subject, each cuff covers a stretch of artery, and the exact points between which measurement should be made are uncertain.

The most interesting results are those of Table V, which gives the pressures recorded from the same two regions when the subject was lying on a bed, but with one leg raised on a support above bed-level. The support extended from heel to thigh so that no sensation of strain was experienced. The relative height to which the limb was raised is indicated by the figures of the second column, which give the hydrostatic pressure of the intervening blood column in mm Hg.

These figures show that, unlike those of the standing posture, the pressures do not always conform to what would be expected from the effect of gravity. The higher the limb is elevated, the more is the systolic pressure, and, to a lesser extent, the diastolic pressure, in excess of the value given by deducting the hydrostatic pressure from the observed brachial pressure. The lowest systolic reading is 76 mm. This behaviour appears in all the subjects, including the young child.

A compensatory mechanism therefore seems to be brought into play to ensure an adequate capillary circulation when a part of the body is elevated above heart level. With regard to the nature of this mechanism one can only speculate. It is not difficult to conceive of conditions which, through better conduction of the pulse-wave, would maintain the systolic pressure at a relatively high value, but the differential diastolic pressure is much more puzzling. Cardiac changes due to the posture may be discounted since they would affect both arm and ankle readings. In any case, the heart rate is very little altered by the elevated position of the limb, in subject A, on whom most of the observations were made, the maximum increase in the experiments where the foot was most elevated, was only 4 beats per minute, or 6% of the recumbent rate. That the pressure determinations are themselves valid seems reasonable (1) from the *a priori* argument that postures can be assumed in which hydrostatic effects would reduce the systolic to a very low and the diastolic to a negative value, (2) because similar effects have been found in the digital arteries, and (3) from Carrier and Rehberg's finding that the capillary pressure, while affected by hydrostatic pressure below heart level, is constant above it. Although the pressure gradient between arteries and capillaries will no doubt alter very materially in the elevated limb positions, the last is very suggestive at least that relative constancy will also be found in the arterial pressure.

In Carrier and Rehberg's view, the constancy of capillary pressure is to be ascribed to the increased friction due to the blood flowing at unusually high velocity through the collapsed veins, and this might also be adduced as the cause of the relatively high arterial pressures. Such an explanation,

in so far as it refers to arterial pressure, seems unsatisfactory. Increasing the peripheral resistance in the circulation, other factors remaining constant, raises both systolic and diastolic pressures, but the latter more than the former, so that the pulse pressure is narrowed. This effect, which is well shown in tonic muscular contraction, is what would be expected from the collapse of the veins suggested by Carrier and Rehberg. In my experiments, on the other hand, the systolic shows more of a compensatory rise than the diastolic and the pulse pressure is broadened. When such a change occurs in the circulatory system as a whole, it is an indication of increased cardiac output. In my experiments it is found as a differential characteristic between the vessels at heart level and those elevated above heart level, but it might be explained on similar grounds, viz., that the distribution of blood is so altered by vasomotor control, that the output to the elevated limb is increased. Moreover, this seems a not unlikely response to a posture which, in the initial moments of its assumption, must lead to deficient oxygenation.

C *Pressures in arteries of different size*

A point that enters into the above comparison of records taken from arm and ankle is the degree to which systolic and diastolic pressures vary with the calibre of the artery from which the records are taken. That there is little difference between the main arterial trunks of the limbs and their primary branches appears from a series of alternate measurements made from the arm (brachial) and from the wrist (radial and ulnar). The averages of these (subject A) gave the systolic as 1.4 mm. lower, and the diastolic 1.6 mm. higher, at the wrist than in the arm. The fall of pressure between arteries and capillaries is in the main confined to the part of the arterial system peripheral to vessels of the size of the radial and ulnar. A considerable diminution has occurred by the time that the digital arteries are reached.

Blood-pressure measurements in the fingers are not, of course, new. Some of the original instruments for recording blood-pressure [Marey (13) and Mosso (14)] were devised to be applied to one or more fingers, but only the point of maximum oscillation was investigated, a point which is now considered to be several millimetres above the diastolic level. This point Mosso found to be 80 mm. Hg in the normal subject.

Measurements of the systolic pressure have also been made by Gartner's (8) method. Using this method, Cohn and Lundsgaard (3) found in eight normal subjects an average difference of 20 mm. between brachial and digital systolic pressure, the values varying considerably in different individuals. Hayashi (9) also found a difference of about 20 mm. in a number of subjects both normal and diseased, while Doleschal's (4) observations indicated somewhat smaller differences. In these determinations, the brachial systolic was estimated by radial palpation, which gives lower results than the oscillographic method, the differences would probably have been some 10 mm. greater in comparison with a brachial systolic determined

oscillographically or by auscultation Gertner's method has been little used, partly because of lack of definition of the systolic point, and partly because of a variability of the readings generally attributed to vasomotor changes

In determining digital pressures with the present oscillogometer, a cuff of the usual armlet form was used, but only 6 cm square This is sufficient to allow of the cuff extending along the greater part of the length of the finger and almost completely encircling it Considerable difficulty was experienced in obtaining satisfactory measurements The amplitude of oscillation is at the best very small and, when the finger is cold, almost inappreciable, in spite of the sensitivity of the oscillogometer, determinations had therefore to be made in an equable temperature at which the subject felt comparatively warm Secondly, with such a small amplitude of movement, any deficiencies in the constancy of the leak become of relatively

TABLE VI

Subj	Aver syst		Aver diast		Differences	
	Wrist	Finger	Wrist	Finger	Syst	Diast
A	124	100	84	58	— 24	— 26
	125	100	86	64	— 25	— 22
					Av — 24.5	— 24
B	126	85	87	45	— 41	— 42
					Av — 41	— 42
C	131	108	91	58	— 23	— 33
	128	100	92	66	— 28	— 26
	125	108	84	68	— 17	— 16
					Av — 22.6	— 25
D	118	90	67	39	— 28	— 28
	111	89	83	58	— 22	— 25
					Av — 25	— 26.5
E	104	74	68	48	— 30	— 20
					Av — 30	— 20

great importance, and the utmost care has to be exercised that there is no drift in pitch due to change in the rate of leakage Lastly, constancy of the rate of leakage cannot by the present system be maintained much below 20 mm Hg and, under certain circumstances, the diastolic pressure in the digital arteries would appear to approach, if not actually to fall below this level Attempts are being made to obviate the last two difficulties by

devising a pressure-lowering mechanism not involving a leak. On account of these difficulties, the digital measurements lack the precision of those obtained from larger vessels.

Table VI compares the systolic and diastolic pressures obtained alternately from the wrist and finger cuffs, the forearm and hand being horizontal and approximately at heart-level.

Allowing for the fact that the wrist systolic is here determined by oscillometric criteria, these figures show, for the systolic pressure, general agreement with the results obtained by Gærtner's method, *i.e.*, the wrist, and hence also the brachial, systolic is 20 to 30 mm higher than the digital, though, in one subject the difference was over 40 mm. They add the information that the diastolic differences are very similar to the systolic. There is, however, much less variability among the individual observations than in the published records of determinations by Gærtner's method, due, no doubt, to the use of a more reliable method.

At the same time there is no doubt that the results can be influenced greatly by vasodilatation. This was shown in the following experiment. Wrist and finger pressures were recorded in subject B, when the hand rested horizontally on the thigh at a level approximately 20 cm below that of the heart, with the following results:

Syst		Diast		Difference	
Wrist	Finger	Wrist	Finger	Syst	Diast
145	105	119	80	40	39

Wrist and hand were then covered with an electric warming-pad and the following series of readings recorded from the finger at intervals of approximately 2 minutes,

Syst	110, 106, 112, 116, 118, 116, 120, 124, 126, 130
Diast	76, 74, 74, 76, 76, 76, 76, 74, 78, 74

Finally the wrist readings repeated gave systolic 144 mm, diastolic 114 mm. As a result of vasodilatation, the wrist-finger systolic difference diminished from 40 to 14 mm, while the diastolic difference remained unchanged.

In another similar experiment in which the finger with its pneumatic cuff was immersed in water as hot as could be borne (47° C), the finger systolic within 10 minutes was only 4 mm Hg below the wrist systolic pressure. The diastolic pressure during this overheating showed a slight tendency to fall.

The increase in amplitude and steepness of rise of the pulse wave is most striking in these experiments, the alterations in pitch at each pulse varying from something which is almost inappreciable with a cold finger to a change, when the finger is warm, which approximates to that obtainable from the radial artery.

Tables VII and VIII show the variations obtained in the finger pressures when the hand is held at different levels above and below the heart, and the relation of these variations to hydrostatic pressure. In the observations recorded in Table VII, the subject sat on an armless chair with the arm and hand (1) at heart level and (2) drooping by the side, in those given in Table VIII, the hand was supported as high as possible above the seated subject.

TABLE VII

Subj	Hydr press	Aver syst		Aver diast		Relation to expected press	
		Heart level	Depend	Heart level	Depend	Syst	Diast
A	43	100	142	58	102	- 1	+ 1
	34	100	134	64	109	0	+ 11
B	44	85	128	55	94	- 1	- 5
C	52	108	165	68	119	+ 5	- 1
D	49	89	139	58	105	+ 1	- 2

TABLE VIII

Subj	Hydr press	Aver syst		Aver diast		Excess over expected press	
		Heart level	Raised	Heart level	Raised	Syst	Diast
A	48	100	86	58	47	+ 34	+ 37
	55	100	57	64	20	+ 12	- 11
B	38	85	62	55	22	+ 15	+ 5
C	50	108	79	68	29	+ 21	- 11
D	48	89	59	58	20	+ 18	- 10

Though the results are not so clean-cut, they confirm what has already been shown in the case of the larger leg vessels. At points in the arterial system below heart level, systolic and diastolic pressures vary in conformity with hydrostatic laws. When a limb is sufficiently elevated above heart level, a compensatory mechanism comes into play to maintain the systolic and diastolic pressures, especially the former, when, by the effect of gravity, they would be reduced to very low values.

This compensatory mechanism is probably a much more potent factor in maintaining the constancy of capillary pressure observed by Carrier and Rehberg than that of the increased venous resistance suggested by the authors themselves.

SUMMARY

A very sensitive blood-pressure oscillometer is described

Records are given of the observations made with the instrument on (1) the relation of oscillographic criteria of systolic and diastolic pressures to the auscultatory criteria , (2) the relation of systolic and diastolic pressures in different parts of the body to hydrostatic pressure , and (3) the values of the systolic and diastolic pressures in the small digital arteries

The comparisons made at different levels in different postures show that the pressures, especially the systolic, in parts elevated above heart level, are maintained at values higher than would be expected from the effects of hydrostatic pressure

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CLINICAL OBSERVATIONS AND EXPERIMENTS RELATING TO
BURNING PAIN IN THE EXTREMITIES, AND TO SO-CALLED
“ ERYTHROMELALGIA ” IN PARTICULAR *

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IN a paper (8) published in the last number of this journal a particular and painful condition of the skin was described and termed for convenience its “susceptible state” This state comprises the following chief characteristics — the affected skin is tender, being unusually sensitive, if not always to pinprick, then to friction and to contacts with water at 40°, even temperatures within the normal range of skin temperature may give rise to burning pain from the affected skin, and similar pain can be induced at lower temperatures by increasing the tension in the skin, as by venous engorgement, or by imposing direct tension upon it Thus it happens that in the ordinary circumstances of life skin so affected gives rise to burning pain particularly when it becomes warm from any cause, when it is rubbed, or, if it is upon the foot, when the limb hangs down The state is in general accompanied by redness, and can be produced in normal skin by burning it, freezing it, scratching it, or by exposing it to ultra-violet light

Such are the chief facts and to explain them a theory has been put forward and is supported by further evidence, that when the skin is in the susceptible state, its tenderness is due to the liberation of a special substance which plays upon the pain nerve endings, it is further supposed that as a result of certain procedures, such as rough usage or arrest of the circulation to the part, the concentration of this substance may rise sufficiently to give continuous burning pain without other interference The evidence suggests that the release of this substance, presumably from cells of the skin itself, is especially apt to occur in association with a state of inflammation This theory is not put forward in a form which in its detail is expected to be final, but at the moment rather as a working hypothesis There can be little doubt of the truth of the central idea of a pain substance what this substance is, how and in what precise circumstances it is liberated to produce pain,

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whether in physiological circumstances it is liberated in a concentration inadequate to produce pain, or whether it is exclusively a product of the inflammatory state, or of a particular phase or form of the inflammatory state, whether or not it is liberated in subcutaneous as well as cutaneous tissues, these are questions that should be subject to closer enquiry and may soon come within the range of profitable discussion. Progress towards the final answers will come by using the theory in its present form as a guide to work, attempting to apply it in explanation of relevant occurrences, and by modifying it to explain unexpected phenomena.

It was stated in the first paper that the observations upon the normal subject were suggested exclusively by similar observations upon patients, in whom the skin of the feet was reddened and tender, but that for convenience of description the observations upon normal skin would be recorded first. That has been done and the present paper gives an account of the completed observations upon the patients to whom allusion was made earlier. The observations and experiments will be described in a series of selected case reports, with such comments as are necessary to bring them into line with the theory. From this description I shall proceed to discuss the more particular problem of so-called "erythromelalgia."

OBSERVATIONS ON BURNING PAIN

CASE 1 Severe urticaria factitia, accompanied by burning pain

D E, a married woman of 26 years complained of a rash and of itching and burning pain in her skin. She presented conspicuous urticaria factitia on all parts of her body.

If the skin of the arm was stroked firmly with a blunt point, the line of the stroke began to give burning pain in 15 seconds, increasing as a prominent wheal developed fully during the next 3 minutes. After about 4 minutes the burning pain lessened and disappeared rapidly. Histamine (1 in 1,000 of the phosphate, freshly neutralised) pricked into the skin gave conspicuous itching, if the histamine wheals were rubbed lightly the itch increased and the patient strongly desired to scratch the skin. There was no sensation of burning, the greater the dose of histamine the greater was the itch. If the skin was stroked lightly, for example with the finger, local redness and a surrounding flare appeared without whealing, in these circumstances itching, exactly similar to that given by histamine, occurred. A little heavier stroke gave slight but distinct burning at about 20 seconds, followed by itching in another 15 seconds, burn and itch would proceed together, but the burn always disappeared first.

If the two arms were heavily stroked simultaneously, the circulation to one being arrested and to the other remaining free, the burning pain was felt more severely and lasted much longer in the former. The burning usually lasted in this arm during the whole of the circulatory arrest (5 or 7 min) and for a subsequent interval, following release, which was about equal to

the complete period of burning in the other arm. Occasionally the burning became unusually intense just after the release of circulation, presumably owing to the accompanying rise of temperature in the skin, similar intensification could be produced by placing the palm of a warm hand over the burning skin.

The observations described were repeated many times.

Comment The sensation usually accompanying urticaria is itching, and this itch has been ascribed to the release of a histamine-like substance in the skin (7). Occasionally, as this patient illustrates, urticaria is accompanied by burning pain, with or without detectable itching accompanying it. This burning pain is interpreted as due to the release of a substance in the skin, which stimulates the pain nerve endings in the skin, and can be held in place by arresting the bloodflow to the part. The substance is not regarded as equivalent to that responsible for itching, but as one less readily released by injury and identical with that postulated in a recent paper (8) to be responsible for the burning pain so often accompanying various inflammations of the skin, following upon relatively severe injuries in normal people, such as burns from heat or a heavy stroke from a whip.

The occurrence in many cases of urticaria factitia, as the present case illustrates, of burning pain rather than the usual itch, within a brief interval of the stroke, brings with it its special suggestion, namely, that the substance released and causing pain may be present as a natural constituent of the cells from which it is released, and that the skin of these patients differs from the normal merely in the ease with which the substance is let loose into the tissue spaces. It suggests that we shall be more correct if we reject the possible view that the pain substance is a special product of the inflammation, to adopt the idea that in the inflammatory state the release of a natural substance is facilitated. The injury to the cells produced by burning heat, severe freezing, or the lash of a whip, may similarly be supposed quickly to give burning pain because of gross damage to the cells concerned.

CASE 2 "Erythromelalgia" so-called and urticaria factitia

A W, * a virgin of 36 years, related that at 8 years of age she suffered from scarlet fever, she was ill for 9 weeks during which time her eyes and hands became puffy. This puffiness returned a little from time to time during the next 5 or 6 years. While convalescent from scarlet fever, a red patch appeared around the right eye and was diagnosed as erysipelas, it lasted for 6 weeks but returned repeatedly for short periods during the next year. At 17 years she had synovitis of the right knee joint, but quickly recovered from it. At 21 years the left knee joint became swollen and painful and she has been ill ever since at the time she was suspected to have a tuberculous

* I am indebted to Dr. Parkes Weber for this case, which he has already briefly reported (19).

joint Her left knee was permanently damaged She was treated with injections and from these she dated her urticaria, which began about her 24th year The malady for which she came under observation began about her 25th year and consisted first of an attack of redness and pain in her left foot without swelling in the same year her right foot was swollen for a few days on several occasions, redness and pain in this foot developed in her 27th year In her 28th year the sheath of the left femoral artery was stripped off, but no benefit followed The condition of redness and pain had become established in both feet, but especially in the left Although the left foot did not swell at first it became swollen repeatedly for a few days or weeks from her 29th year onwards In her 31st year she had trouble with the left shoulder joint and in her 33rd year her right knee joint became swollen and its movement subsequently limited During her 36th year her hands began to give similar trouble and a little later the skin of her face and chest was affected Her symptoms had always been worse in winter and better in summer but had otherwise increased progressively Her complaints when under observation were as follows —

Her left foot troubled her more than her right, she suffered from a continuous, throbbless pain, described as "burning," felt especially across the base of the toes on their plantar aspect If she rested in a cool room with her feet up the pain would go away She avoided warming the feet never allowing a hot bottle to come near them, keeping them away from the fire, and washing them in tepid but not in hot water owing to the pain induced in them by heat She stated that the pain was induced in her feet by the simple act of hanging the feet down out of bed and by walking on them, so that to walk more than 100 yards had become very difficult The burning pain was preceded usually by ache If the pain continued it spread to the rest of the sole, to the dor-sum of the foot and eventually to the ankle, it was often very severe, causing her great suffering The right foot was similarly but less affected

The burning pain in her hands was chiefly experienced in the palms of the hands and was worse when they hung down or were warmed in water or by a fire She described it as identical in character with that in the feet The facial pain was in the region of the brow and the tissues around the right eye, which tissues became red and swollen from time to time, when first experienced the swelling and redness lasted a month, and she could hardly open her eye Similar though less frequent pain occurred around the left eye, without swelling The facial pain was burning in character, the pain in this region and in this only was often throbbing Burning pain had been experienced occasionally in the skin over the upper and front area of the chest where the skin was reddened by exposure Both the pain in the hands and that in the face might be severe

It is to be noted that while the patient stated that her symptoms were worse in winter than in summer, and on cold than on warm days, she recognised that warmth aggravated and cold relieved her pain at a given

moment Thus she could walk out of doors without pain on cold days, but would suffer unusually on returning to a warm room

The patient was examined many times in both winter and summer months and was under daily examination for a period of several weeks during the summer A general account of her state and of tests made upon her will be given, it being understood that the result of no test is described that was not repeatedly witnessed She was a thin woman of placid temperament, and presented no signs suggesting disease of the nervous system or heart, her digestive system seemed in good order, she was closely searched for focal infections and none were found Her urine was normal The plasma calcium was normal, being 9.7 mg for 100 cc The patient gave a positive tuberculin skin test, there was the usual delayed reaction, but no immediate response Her trunk and neck were diffusely overpigmented, but in a few places there were patches of unpigmented skin, one on her left forearm was particularly conspicuous and was stated to have followed after a red swelling, the pigmented and unpigmented areas were sharply marked from each other, as is usual in vitiligo, by crenated margins

Her hands and feet were habitually cold, the temperature of the fingers and toes being repeatedly found to be but a few degrees above room temperature even in the warm weather of mid-summer, when her body was hot and moist with sweat The coldness of her limbs was a quite definite abnormality She believed that her hands and feet were usually warm, but this belief was quite erroneous, subjectively she could not detect if her feet were cold, cool, or warm, she knew only that they burned or did not burn The unusual coldness diminished when traced from fingers and toes upwards but was present in some degree in the forearms and legs Her facial skin was usually warm or hot While lying horizontally, the dorsal surface of the left foot was more deeply coloured than normal, the minute superficial vessels being visibly dilated, the colour was diffuse and patchy, mostly cyanotic (Colour XI, of the scale previously published (5)), but here and there interspersed with a redder tint The parts of the soles of the feet that take pressure were redder than normal, the feet were nearly always wet with sweat The malleoli and the inner side of the foot were also discoloured, but the outer side and toes presented little change The skin above the ankles was coloured normally The skin of the shin and of the dorsum of the foot was glossy, it was thrown into fine wrinkles when pinched up These parts and especially the instep had been much swollen a few months before The foot was very tender to pressure and to rough friction, especially the plantar aspect of the bases of the toes, and the dorsum, tenderness and discoloration were closely associated on the dorsum Once during a period of rest in bed a tender bruise appeared without obvious cause on the dorsum of the right foot, the patient spoke of others experienced The skin was not hypersensitive to cotton wool touches or to needle pricks The foot was in every respect well formed and the nails normal The right foot was similarly but much less discoloured Both,

but the left especially, became much deeper in colour when hung down. The femoral, popliteal, posterior tibial and right dorsalis pedis pulses were normally full, the left dorsalis pedis pulse could be felt when the foot was warm, as could a second pulse from a vessel lying outside it. The vascular channels to the feet were adequate, the skin of the toes showed clear capillary pulsation when heated artificially to 42°C and when spontaneously and fully warm.

The hands, with their nails, were well formed, and the skin everywhere supple, they were cold and moist, their palmar surfaces were redder in colour than is usual, and tender to pressure. The radial and ulnar pulses were easily palpable. Capillary pulsation was vivid in all the finger tips after soaking the hand in hot water. The facial skin was high in colour, as was that of the neck and upper part of the chest in front. The face was usually very warm and often displayed spontaneous capillary pulsation.

The pain and its relation to temperature. It soon became clear, in making observations upon this patient, that pain and the temperature of the skin in which it was occurring were related. With the left foot hanging down in a bath, the temperature of the water was raised from 27° very gradually, burning began at 29.1° and was unpleasant at 33° . Immersion of a hand or foot in water at 35° after a preliminary bath of 20° to 25° gave almost immediate burning pain, moderately severe in the case of the left foot, decreasing a little after a few seconds, but continuing less severely for long periods. Thus in special tests, in which the horizontally held hand, or the brow, was maintained at 31° pain of moderate intensity continued for 10 minutes, though declining distinctly by the end of this period. The transference of the limb while painful from water at 35° to 20° gave almost instant relief, the pain vanishing entirely in 5 to 7 seconds. The burning pain experienced on immersing the foot in warm water was stated to be precisely like that of which she came complaining, both in its character and in its site. A rise of temperature from 20° to 28° , by changing from one bath to another, gave no pain, but a rise from 27° to 35° (also a rise of 8°) gave much burning, and a rise from 32° to 40° gave almost intolerable burning. Not only the steepness of gradient, but the actual temperature reached mattered.

Extensive tests were undertaken to ascertain what parts of the skin were unusually sensitive to heat. Parts of the body other than the hands and feet were tested by means of a cylindrical bar of copper (5 cm diam). Two of these cylinders were kept in a water bath at 40° and alternately were quickly dried and the flat ends applied for 3 sec to the skin. In normal subjects such cylinders produce on skin that is usually exposed to the air a sense of pleasant warmth, and they feel hot, but not uncomfortable, when applied to the skin of the trunk. This is a convenient form of test and should prove valuable in many circumstances. In the patient, the application gave intolerable stinging pain in the feet, it gave severe stinging pain on the brow and over the malar processes and palms, these were the areas in which spontaneous pain was

frequent It gave considerable sting over the back and neck and over the skin covering the upper part of the chest, where it was reddened by exposure It gave a sensation of heat with or without slight sting over the greater part of the trunk Where the application of heat produced stinging pain it almost always left subsequent redness, though there were a few exceptions in which pain occurred without reddening or reddening without pain It will be noticed that those parts of the skin giving rise to spontaneous pain and an unusually red response to warmth applied were areas exposed directly to the atmosphere, or under the thin covering of stockings, in ordinary circumstances It is to be added that over the same areas cold cylinders (at 0°) gave stinging pain too, the feet, palms of hands, legs, forearms, chest and brow were especially sensitive In the feet temperatures as high as 18° gave stinging pain

It did not matter how a rise of temperature came about, if the level reached were adequate, pain would follow Lying at rest in bed, on cool or warm days, with hands and feet exposed or lightly covered, this woman was in no discomfort, and her hands and feet were then found to be cold When pain in a hand or foot occurred spontaneously, then this extremity was found to be warm or hot On several occasions during a period of warm weather the vasomotor tone in the limbs of this patient was deliberately released by heating up the body For a period of an hour she lay covered by nightdress and sheet only, with hands and feet exposed Thermal junctions were then fastened to fingers of the two hands (base of nail) and to the bases of the toes both dorsally and ventrally At a room temperature of about 25°C vascular relaxation would eventually occur in some parts of the extremities, or at lower room temperatures it would be expedited by placing a hot electric pad on the abdomen and covering the pad and patient's trunk with layers of blanket, or by heating the whole trunk in a warm chamber, the air of which was raised to 55° In this way the rises of temperature occurring in fingers and toes on the two sides could be compared readily with the appearance of pain in the same regions In these experiments, as the body warmed and vasomotor tone declined, the extremities would gradually become warm It was the rule, as it is in normal subjects, for the hands to become warm first, the fingers becoming warm at their tips and the warmth spreading up the finger into the palm of the hand Burning pain came in the fingers after they had gradually warmed to about 30° or a little more, and gradually increased in severity and spread to the hand as this became hotter The feet warmed up much later It was the rule for the temperature to rise first over the outer part of the left foot and here pain would first appear The warmth, and subsequently the pain, would spread along the outer side of this foot to the heel, would involve the whole sole, the toes in their length, and lastly the dorsum of the foot Similar events in the right foot were always more delayed It was manifest that the rise of temperature preceded pain in the foot as in the hand The pain was limited to, and always appeared in, parts that became sufficiently hot,

the requisite temperature was usually about 30° or a little more. Thus there was a sequence in which the different parts of the two feet became warm and there was the same sequence in respect of pain, this relation was abundantly illustrated in a number of observations.

Hanging the limb down and its effects on colour, temperature and pain

On a number of occasions many observations were made upon the effects of hanging the feet down. One change was invariable. The skin of the feet, and especially the left one, became deeply engorged with blood. At first the colour might be bright red (Colour VII or VIII), and especially so if the feet were cold, over a large part of the dorsum of the foot, more often the colour was patchy red and purple, the colour became more cyanotic with time. The veins became swollen if the foot was warm before hanging it down but showed little distension if cold. In no instance did the arterial pulsation in the foot change appreciably with dependency. The temperature of the foot might change a little with dependency, but the change was insignificant, and inconstant in amount and in direction. Although the foot always became engorged when hung down, pain sometimes appeared and sometimes did not. The appearance of pain was not related to any of the insignificant changes of temperature of the skin just described. The factor influencing the appearance or non-appearance of pain in the foot on dependency was the level of temperature prevailing in the foot during the observation. Usually, the patient could sit or stand with the feet in water at 25° for long periods (10 or 15 min. or more) in comfort, they could be hung down in water at 28° or 29° for a few minutes without pain, but pain would come eventually at these temperatures. A foot hanging down and immersed at 32.5° usually, and at 35° always, gave burning pain coming in a half minute, and rapidly growing in severity. There was little difficulty in finding a critical immersion temperature (about 32°) at which pain would occur with the foot hanging down, but not with the foot raised. Burning pain was exceptionally caused in these feet by hanging them down for 5 or 10 minutes, when the natural surface temperature of the toes nowhere exceeded 25° or 26° .

If, instead of hanging the foot down, it was kept more or less horizontal, while immersed (or soon after immersion) at about 32° , pain was avoided, but could be induced by throwing onto the veins a pressure of 70 to 80 mm Hg. This pain had the same character and situation as that experienced on hanging the limb down and was relieved at once, and abolished within a few seconds, by releasing the venous outlet. The burning pain brought on by hanging the foot down or by throwing pressure onto the veins, was stated to be relieved within 2 or 3 seconds if a comparable pneumatic pressure was thrown upon the painful skin. This was usually the skin at the bases of the toes and the counter pressure was exerted by wrapping a pneumatic cuff snugly around them and inflating it, the pain would return again within 1 minute or less of the release of this counter pressure. Similar results were obtained in the case of the hands. These observations show how pain

induced by dependency in this patient resulted from a passive increase in the tension of the vessels and surrounding tissues. This is almost certainly the proper interpretation of the results, especially if we take into consideration similar tests on the ultraviolet light burns of normal skin (8). But in this particular patient the idea arose that relief was due, in part, to confusion owing to sensations resulting from the pneumatic bandage. When burning pain is slight, such confusion sometimes presents a very real difficulty, the sensations arising from the bandage tending to conceal the burning pain. In our patient, however, the phenomenon of relief of pain in a dependent limb by counter pressure seems beyond doubt, as it was always strictly confined to the part actually pressed upon, and the pain relieved was often severe. This further statement is necessitated by the fact that this patient spoke also of relief by counter pressure, when pain in the skin had been provoked by friction, the limb being then horizontal, but such relief was spoken of as only partial if the original pain was severe, and, if it was mild, relief could be obtained whether the pneumatic bandage was applied actually over the lesion or merely in its immediate neighbourhood.

To sum up, it has been proved that in this patient there was a "susceptible state" of the superficial tissues of the feet. Pain could often readily be induced in the feet by allowing them to hang down. The conditions requisite to provoke this pain were two in number, first an adequate temperature (usually lying between 30° and 35° on different occasions), and adequate stretching of the vessels under hydrostatic pressure. The pain of dependency was ultimately determined by tension in susceptible tissue that was warm, it was not caused by a "vasomotor storm," nor directly or indirectly by any nerve reflex associated with the assumption of an erect posture.

In concluding this section the following protocol of an exceptional observation is given to illustrate how readily the events occurring in relation to posture may be misinterpreted if full and exact observations, with knowledge of the factors involved, fail to be made.

Protocol. On one occasion this patient walked to the hospital on a cold day. The colour of the left foot was as usual, but the instep was swollen. The feet were cold from the ankle downwards (toes 22° to 23° and room temp 18.5° to 20°). The patient rested a half hour with feet elevated and without pain. A thermal junction was fastened to the base of the left toes.

Min after entering	Temp of toes	
30	23.3	
40	26.0	Patient still horizontal, the foot has warmed spontaneously
41		Foot allowed to hang down, it soon starts to ache and it becomes deeply mottled with red and purple colour
44	27.9	The ache continues
50	30.0	Although the temperature of the base of the toes has been increasing for 20 min there is no burning
53½	30.5	Burning pain starts in toes
63	32.0	Pain has steadily increased
64		Foot raised to horizontal
65	32.0	The pain is better, the foot is paler
72	32.5°	Pain has gone
93	31.8	Slight burn in sole of foot which is warmer than toes which are without pain

109	33 0	The burn in the sole has gone
114	33 2	No pain, feet lowered to floor, burn starts in the toes within a half minute
115		Feet raised to horizontal Pain eased at once
116	33 0	Pain gone
124		Feet lowered to ground Burn across toes quickly develops
128	31 7	The pain has steadily increased in the dependent toes although their temperature has actually fallen
128		Feet raised to horizontal, giving almost instant relief
130	32 2	Still a little burn in the toe

This protocol illustrates again how burning pain may be induced by hanging the feet down, and how it may be relieved by raising them, but it also clearly shows that the pain is not part of an attack in which the bloodflow to the feet is increased. The position of the foot did not influence its temperature, which at first steadily increased whether the foot was up or down. The protocol, however, is particularly interesting because it is obvious that, with fewer observations, the initial rise of temperature, before the patient's feet were first lowered, could readily have been overlooked, leading to the events witnessed subsequently being interpreted as an attack of vasodilatation of the feet with pain, induced by the dependent posture. Actually the correct interpretation is very different. The patient had been exposed to cold outside air and came cold into the room, she warmed up slowly but normally and the vessels of the feet gradually relaxed, this process, already well advanced, continued after the feet were allowed to hang down, and there came a time when the temperature had risen sufficiently to produce pain in feet that were congested. At this stage pain in the feet could be controlled by changing their position.

Pain induced by friction, with and without occlusion of vessels It was known to the patient and readily confirmed by observation that rubbing the tender skin of the feet and certain other affected parts induced burning pain in them. During the rubbing pain was experienced but quickly passed away, to return about 10 or 15 seconds after the last of 5 quick firm rubs of the skin. This returning pain lasted for about 3 to 5 minutes and was confined to the area rubbed, changing in location with the latter. If the circulation to the leg was stopped before the skin was rubbed, the burning pain once established lasted as long as the circulation was obstructed (5 or 6 min), and, though decreasing or disappearing temporarily soon after the circulation was released, would reappear to disappear finally about 3 or 4 minutes after the release.

These observations were carried out on the feet previously warmed by immersion and in the horizontal position. The areas of skin used were at a temperature of about 27° to 30°. The observations are considered to show that friction brings into the tissue spaces a substance, which acts on the nerve endings sufficiently to cause them to discharge pain impulses under ordinary conditions of temperature, etc. The experiments led to two further observations. First, they showed that friction of the affected skin, with unimpeded circulation, in this patient raised its temperature unusually

(by about 3°), the raised temperature lasting also for unusually long periods. Secondly, it led to the discovery that this patient had a general urticaria factitia, of which more may be said.

Urticaria Urticaria factitia was readily produced over the whole trunk and proximal part of the limbs, on the lower forearm and leg, and on dorsum of hand and foot it was inconspicuous. On the trunk the wheals were very prominent. On the limbs, which were cool, the wheal was accompanied by an unusually large rise of temperature, 2° or 3°, and this rise of temperature lasted unusually long (more than 20 min in some instances). A very light stroke produced reddening and itching, with little whealing, the heavier stroke, gave conspicuous whealing always accompanied by burning pain. Sometimes the reaction would start with itching and continue with a mixture of itching and burning. A single firm stroke with a blunt point across the forehead whealed it distinctly and gave burning pain, accompanied by throbbing which was found to be synchronous with the pulse beats, the pain sometimes lasted as long as an hour and was described by the patient as identical with her usual facial pain. Yet her usual facial pain was unassociated with whealing though often accompanied by redness. Severe burning followed for 5 minutes after stroking palate, tongue and mucous membrane of the cheek. Neutralised histamine acid phosphate solution (1 in 200) gave severe itching but no burning, when punctured into the skin of the arms.

On the forearm the burning pain following a single firm stroke was moderately severe and lasted about 3 to 5 minutes. If the arm vessels were first occluded, and the skin then stroked and subsequently kept at about 35°, the burning pain would last usually* to the end of 5 or 6 minutes occlusion. At the release the pain would disappear but almost always* returned within a minute or two of release, to disappear usually about 4 to 7 minutes after release. It was interesting to note that skin that had been whealed became very susceptible to heat, a copper cylinder at 40° producing burning pain in an area of skin as long as 40 or 50 minutes after it had been stroked.

These observations were in the main similar to those made upon Case 1, and similarly indicate the release of a substance causing burning pain, by a single stroke of the skin.

Urticaria could not be elicited by the application of warm (40°) or cold (0°) cylinders for varying times.

Pain induced by simple occlusion In these experiments it was necessary to maintain the temperature of the skin at an adequate point (32° to 35°) effected most easily by immersing the limb in water. It was also necessary that the limb should be emptied of blood by raising it before the circulation to it was arrested, and that the arrest should be complete, otherwise increased tension of the blood in the venous system interfered with the result. To

* Occasionally and inconsistently the pain would end a little before the end of such an occlusion, and it did not always return afterwards. The reason of variation is unknown.

arrest the circulation an unusually wide pneumatic cuff, covering the elbow or knee joint completely, was used and no observation was accepted in which tension in the veins of the limb rose appreciably. It was found, in a limb so treated, that burning pain began gradually in foot or hand in about 2 to 5 minutes, and having begun increased steadily in intensity, on release of the circulation the pain would vanish, usually in a period of about a half minute or a little longer. In the case of the feet immersion was impossible without some degree of dependency, in the case of the hands, in which the result was similar, dependency of the part was avoided.

From these observations it is concluded that a substance, bringing the nerve endings into a condition in which they more readily discharge sensory impulses, gradually accumulated in the more severely affected superficial tissues of this patient during the period of vascular occlusion, suggesting that in these parts this substance was being constantly formed and released into the tissue spaces.

Comment. The patient here described suffered from a peculiar condition of the skin affecting mainly her four extremities, but especially her left foot. This condition was one in which burning pain, often severe, occurred in association with increased bloodflow to the limb, and was aggravated by heat, decreased by cold, increased by dependency, and decreased by elevation of the limb. This is a group of symptoms corresponding closely with what has been called "erythromelalgia."

It will be obvious from what we now know that the explanation of these phenomena may not be left at a mere name. It has been shown that the attacks of pain were produced by anything causing the affected skin to become sufficiently warm, as when the foot was immersed in warm water or when the vessels of the limb were dilated as a normal response to warming the body. The characteristic relation of pain to temperature, the tenderness, the relation of pain to vascular tension at certain temperatures, the production of lasting pain by friction, or by simple occlusion, and the prolongation of pain caused by friction when the circulation was arrested, are all consistent with the view that the skin was in a state identical with what has been termed the "susceptible state." That is to say, the condition giving rise to symptoms is a morbid condition located in the skin itself. That is the important first conclusion at which we definitely arrive.

As to the nature of the local process, that can only be discussed speculatively. The "susceptible state" has been regarded as one associated particularly with inflammation. The occasional occurrence of redness and swelling in the parts of the patient's skin giving rise to spontaneous pain, and subsequently found to be especially susceptible, lends support to the idea that the essential condition in these tissue areas was one of local (residual or chronic) inflammation. The underlying cause of this supposed inflammation remained obscure. The susceptible state was not confined to, though it was most prominent in, the parts of the skin that were habitually cold, so that, although damage by persistent cold might be regarded perhaps

as contributory, it was not alone responsible. There was evidence of a similar though slighter affection of much of the skin of the body. Urticaria factitia was also present in severe form and the wheals were associated with burning pain. It might be suggested in explanation of the susceptible skin of hand and foot, that this susceptibility was due to an inflammatory condition in which a specific pain substance was being released and acting on the pain nerve endings, it *must* be suggested that the skin as a whole and also mucous membranes were unusually prone to mechanical injury and that single firm strokes would release the pain substance. It seems very likely that in the patient described the susceptibility of the skin and its proneness to urticaria were closely linked together from the standpoint of causation and that ultimately a hypothesis may be put forward that will readily explain both phenomena, but this explanation will not come until we know far more of the ultimate factors underlying such states as urticaria factitia.

The observations upon this patient have brought two suggestions relating to skin in the susceptible state, both of which require further investigation. Firstly, in this patient, as in some others, it was noticed that considerable pain would continue for long periods in skin which was kept at 34° to 35°, the skin of the brow, or of the hand kept horizontal, being used to avoid passive congestion. These observations suggest that such a temperature in this case may have been capable of causing the concentration of liberated substance to rise above its ordinary level.

Secondly, it was noticed that the skin of the feet first to become warm or hot in a general vasodilatation such as is induced by warming the body, was the skin showing the susceptible state most clearly. This suggests that the vessels of susceptible skin are prone to respond with unusual readiness to vasomotor (dilator) influences, a matter that is relevant to the supposed association of pain and vasodilatation in the affected limb.

CASE 3 Painful redness of the feet (erythrocyanosis)

D S, an unmarried seamstress of 20 years came to hospital complaining of trouble in her hands and feet.

The hands presented characteristic signs of mild Raynaud's disease, present for about 4 years. Firm strokes of the skin of the trunk gave distinct whealing but no more than is seen in many healthy young people. The whealing was accompanied by neither burning nor itching of the skin.

The feet were in a different state, in these, attacks of whiteness, blueness or numbness had not been experienced. For about 4 years her feet had become swollen and painful from time to time. The feet would ache a lot and become burning hot after walking about 2 miles, at first this was noticed in the summer time, but later in the winter time as well. When directly questioned she stated that burning pain was experienced whenever the feet became hot, as when walking on a hot day, when they became warm after being very cold, or when standing or lying in a hot bath. She avoided walking

on very cold or warm days, and gave up hot baths, so as to escape pain. At rest her feet were almost always cold and she was then without pain. Pain was rarely felt in bed, but her feet were rarely warm in bed. The left foot was first affected, the right foot became painful to a less extent. The pain was described as a continuous burning without throb, and was felt over the lower leg and ankle, in the balls of the toes, along the inner side of the arch and over the instep, areas that were discoloured.

The feet were well formed, their arches were normal. They were cold and much discoloured, the vascular colour of the skin being abnormally deep and cyanotic in tint (Colour XIII). The discoloration was distributed in diffuse tender patches, especially on the dorsum of the foot where unprotected by shoe, the left foot was more discoloured than the right and tender. A large discoloured patch on each instep ended abruptly below in a sharp border marking out precisely the area protected by shoe. The soles of the feet were unusually horny for a young and well shod woman. Her habit was to wear thin artificial silk stockings, low shoes, and a skirt coming to the middle of the calf of the leg. The lower parts of both legs were deeply coloured and cyanotic. A little œdema was once found below the left internal malleolus. The dorsalis pedis and posterior tibial arteries pulsed normally. The discoloration described was best seen while the patient sat, when elevated the feet were relatively pale, reddening quickly and deeply when hung down and then gradually assuming a purple tint. If the feet were warm the veins became swollen when hung down, but the arterial pulsations were no greater than before and the measured temperature of the feet remained unchanged.

On one occasion when the feet were cold, the temperature of the skin at the bases of the great toes was found to be 22.0° at a room temperature of 17.8° . She began to walk quickly up and down the wooden floor and continued to do so for nearly an hour, the temperature of the toes gradually rising to about 29.5° . She then complained that the feet were beginning to ache and shortly to burn, these being her usual sensations. The burning was described as being in the plantar surface and over the instep. Ten minutes later, the pain having increased, she stopped walking, and the temperature of the toes had risen to 30.0° or 30.4° , the pain disappeared gradually when she rested and simultaneously the feet became cooler.

After she had rested, she sat with the two feet hanging down and immersed in water at 28.5° , in which they were quite comfortable. The temperature was steadily raised at about the rate of 0.5° a minute. Tingling was experienced in the left foot when the water bath was at 30.9° and burning pain began at 31.0° . The right foot began to burn at 33.3° , the burning in the left foot increasing. Burning pain was uncomfortable in both when the temperature had risen to 37.8° . If either of the feet was transferred to a bath of water at 37° to 40° , after a preliminary bath at 25° to 30° , burning pain started in about 10 seconds. This pain, once established, continued and might even increase while the foot was immersed. The copper cylinder, either at 40° or at 0° ,

gave stinging pain when applied over the dorsal surfaces and soles of the feet, pain of less intensity over the insteps and legs and over the palms of the hands, very slight pain over the thighs and the back and front of the chest, and no sting over the face and arms

Friction elicited tenderness of the dorsum of the left foot, but this pain soon passed away, to return a little later and to last for one, to one and a half, minutes. If the circulation to the foot had previously been arrested, the pain following friction was much intensified, lasted as long as the circulation was held up (5 min) and disappeared to reappear again for a time after the circulation was released again.

Simple arrest of the circulation sufficed to induce burning pain in either foot after an interval, and this pain increased steadily until the release, but the pain so induced was less intense and much slower in coming than in the friction experiment previously described.

Comment The burning pain in the feet experienced by this patient evidently resulted, mainly at all events, from a simple rise of temperature in the affected parts, the pain was provoked by applying external warmth or by warmth conveyed to the feet by the increased bloodflow induced in them by walking.

Closer examination showed that the skin of the feet in this patient was in what has been called the "susceptible state," displaying the characteristic reactions of such skin to warmth, to cold, to friction, and to circulatory arrest. This case, commonly classed as "erythrocyanosis" might be interpreted as one in which the susceptible state of the skin arose out of chronic inflammation resulting from repeated exposure to cold. From our present standpoint the case has more importance as being a clinical type distinct from the last case described and as such it begins to illustrate that the "susceptible state" is not peculiar to what may be regarded as a single disease.

CASE 4 Painful redness of the feet (erythrocyanosis)

E. P., an unmarried, nervous and introspective woman of no occupation and of 21 years, came to hospital complaining of discoloration of hands and feet and of pains in the latter. From childhood she had noticed unusual coldness of hands and feet, especially in cold weather. Gradually from the age of 14 years her hands became discoloured, being deeply red or blue, as high as the wrists. When the hands were for long blue and cold, they subsequently became puffy, and she was unable to make a fist properly. The fingers ached when cold. The hands were seen to be characteristic of what has been termed acrocyanosis, being cold, deeply coloured and cyanotic as high as the wrists, the nails were in perfect condition and the texture of the skin normal. When immersed in water at 40° the backs of the hand and the fingers burned.

Her feet had been painful for 3 years. The left foot was the more affected. There was a continuous dull ache in the feet, occurring sometimes

while she walked, sometimes while resting, and even waking her from sleep. Her chief and latest complaint was of burning pain, coming occasionally over the insteps and front of ankle. With this burning pain the feet seemed to be hot. This pain was experienced especially after exercise or shortly after lying down to rest after exercise. Sometimes the skin in front of the ankles would crack a little where discoloured and bleed a little. Occasionally chilblains occurred on the fingers and toes in winter, during which the feet troubled her more than in summer. The malady had been progressing unfavourably. It was her habit to take tepid but not hot baths. She wore short skirts and thin stockings the year round.

The legs were discoloured from the knees downwards, this vascular discoloration was diffuse, and of gradually increasing intensity when traced from knee to ankle, where the depth of colour was full. The dorsal surfaces of the feet were also deeply affected, except where the shoe protected the toes and the strap crossed the instep. These parts were almost normal in colour and sharply marked off from the rest. The tint of the affected skin was cyanotic (Colour XII). The colour became deeper and more cyanotic when the legs were allowed to hang down. The skin of the feet and legs was cold, where discoloration was most conspicuous. Namely, over the left instep and ankle, it was very hypersensitive, the patient shrinking from all contacts, even from touches with cotton wool. The right foot was not hypersensitive to touches, but only to rough friction. The skin around the malleoli was sometimes distinctly infiltrated, pitting slightly on pressure. The arterial pulses were all palpable in the feet.

When emotionally disturbed this girl blushed very deeply, the whole face and neck becoming deeply suffused, on one occasion, being disturbed while her feet were exposed, the cyanotic skin was seen to participate in the blush, becoming vividly red from the knees to the feet. A subcutaneous injection of histamine produced similar blushing of face and legs.

The feet were allowed to hang immersed in water at 28° and the temperature of the water was gradually raised, burning pain came in the left (the worse) foot at 28.8° and in the right foot at 30.4° . Transference of a foot from water at 20° or 30° to 38° or 40° gave burning pain within a few seconds, the pain was induced more easily, came quicker and was more intense in the case of the left foot, but was present in both, it came quicker and was more intense when the initial bath was at 30° than at 20° . The pain continued, though lessening in degree, while her feet remained in water for 5, 8, or more minutes, it was relieved in a few seconds by reimmersion in the cool bath. The burning pain occurred over the dorsal surfaces of the feet and was stated to resemble precisely the pain experienced after exercise. The effects of increasing venous pressure on the pain in the foot were studied but no conclusion could be drawn.

Firm strokes on the skin with a blunt point produced slight whealing of the skin of the arms and trunk, but not much more than is found frequently amongst young people. The stroke was followed after 15 to 30 seconds by

slight but definite burning pain in the skin, lasting about a half minute. If the circulation to the skin was arrested before the stroke, the burning lasted about twice as long and was much more intense, moreover it often returned after the bloodflow to the limb had been restored, in this respect, however, (as in Case 2) the results for some unexplained reason were not entirely consistent. Histamine acid phosphate, neutralised, and at a strength of 1 in 200, gave pure itching when pricked into the skin, but no burning.

Comment This case is in many respects similar to the last described and, so far as the feet are concerned, is to be interpreted similarly. It is another clear example of the "susceptible state" in skin of the feet and lower part of the legs, in a patient suffering from what is ordinarily called "erythrocyanosis". The hands were similarly affected in minor degree. But the patient also suffered from a mild urticaria factitia accompanied by burning pain, a fact which brings her condition into closer accord with that of Case 2.

CASE 5 Painful redness of feet due to chilblain

D S, a domestic servant of 25 years had suffered for ten years from irritation and pain over both her insteps and lower legs. The condition was most prominent in cold weather and had gradually become worse. The right foot was more affected than the left. Her feet had always been cold. Itching came in attacks during cold weather, was severe, and soon followed by redness, swelling, and tenderness, sometimes small blisters would appear in the reddened areas. These attacks usually occurred in the day time, and itching was greatly aggravated by the warmth of her bed at night. Her pain was of two kinds. Her chief complaint was of burning in her feet, experienced when the feet became warm in bed or on putting them into hot water. She was sometimes forced to get up at night to obtain relief from this burning pain. The pain was often severe, was aggravated by allowing the feet to hang down and relieved by raising them. Usually the pain was a continuous unchanging one, occasionally it was accompanied by regular throbbing. She also complained of tiresome aching of the feet, especially after long standing, this was relieved by rest and especially by the horizontal position.

When seen, large patches of discoloured skin were found on the right side in front of and behind the ankle and over the lower part of the front of the leg itself. These patches of discoloration were from 4 to 6 cm. in diameter, irregular in outline and diffuse at the edges. The colour was a deep red and deep blue, mottled together. These areas were swollen and in places distinctly nodular, they were extremely tender, like the rest of the foot they were cold to touch. The left foot was similarly but less severely affected, it also was cold.

When the feet were transferred from a preliminary bath of water at 20° or 30° to 40°, burning pain occurred within a few seconds. It was her usual pain and was felt in the usual parts, namely the discoloured areas of skin. The pain occurred earlier and was more severe in the case of the right

foot than of the left, it was more severe when the foot had been transferred to 40° water from 30° than from 20°, it lasted, though gradually declining, for a few minutes during immersion in the warm water. Deliberate congestion of the veins aggravated the burning pain induced by warmth, and like dependency greatly increased the depth of colour of the affected skin.

Comment In commenting upon this case emphasis is laid upon the presence of the "susceptible state" in the skin of the feet of a patient suffering from a chronic condition resulting from the type of inflammation ordinarily termed "chilblain."

CASE 6 Burning pain provoked by warmth and by dependency, in a gangrenous toe in thromboangitis

S. D., a laboratory assistant, first complained at 36 years of age of intermittent claudication. He was unable to walk more than 100 yards without aching pain in the calf of his right leg but relief came quickly with rest. In his 38th year an ulcer appeared on his right heel. The right femoral artery was stripped of its adventitia by a surgeon, gangrene of the foot followed, and the leg was amputated, first below the knee and through the thigh a fortnight later. In his 40th year an ulcer appeared on the 3rd toe of his left foot, and destroyed the toe, a month later the 2nd and 4th toes became discoloured and ulcerated, and a black scab appeared under the nail of the 1st toe.

When seen, in his 40th year, the 1st toe was reddened and scarred at its tip. The skin was reddened over the dorsum of the foot opposite the bases of the 2nd to 4th toes, and the 4th toe was ulcerated on its mesial aspect, the 2nd toe had healed, the 3rd toe was missing. The depth of the redness of the foot was much intensified by hanging the foot down. No arterial pulsation could be felt in the leg below the level of the superficial femoral vessel. The foot was warm with the exception of the end of the great toe. The veins of the foot were numerous and well displayed. A reactive hyperæmia test showed delay in the return of blood to the whole foot and especially to the toes.

The pain was described as sometimes stabbing, but usually a continuous burning pain, occasionally it throbbed regularly. The burning pain was severe, starting over the 4th toe and spreading over the instep and often up the leg. It was described as similar to that experienced in a finger that has been crushed. A little aching or smarting sensation was always present, but the severe burning came in attacks night or day and often without explanation. Hanging the foot down produced a very persistent and intense burning, relief was usually obtained by lifting the leg to a horizontal position. The warmth of the bedclothes would start the pain and relief would be obtained by moving the foot to a cooler place in the bed. Hot water bottles in the bed were found to be intolerable, and the foot had not been placed in hot water for many months, because of the excruciating

burning sensation which would be provoked and which would last perhaps an hour

Comment The man's account of his symptoms was so clear and the pain experienced so severe, that no temperature tests were employed. His case exemplifies a frequent symptomatology of gangrene of a toe, the burning pain, brought on by warmth and dependency and relieved by cold, is attributed to the inflamed tissues of the toe being in the "susceptible state"

CASE 7 Burning pain in gangrenous toe in case of senile arteritis

F C, a commissioner, and an alert and intelligent man, first complained of pain in the calf of the left leg after walking half a mile in the month of January, when 53 years old. This symptom increased in severity in a few months until he could walk no more than 50 yards. By July, the left great toe became unusually red and one day, when he placed it in hot water, it rapidly became "black", the circulation to this toe was evidently so deficient at the time that heating the toe resulted in rapid deoxygenation of the blood circulating in it and profound cyanosis, this phenomenon is seen occasionally when digits are supplied by arteries that are diseased and incapable of appreciable expansion. In August this toe was painful, it was dressed with Iysol, and soon became ulcerated around the nail. In September the nail was removed and the toe began to heal.

He was first seen in December of the same year, complaining of severe burning pain in the toe, experienced especially in bed at night, relief was obtained by hanging the leg outside the bedclothes. The pain was described as horrible, being a continuous steady burn of great severity, without throb, coming gradually and going away very gradually.

The patient was a well preserved man, showing tortuosity of the brachial arteries, and blood pressure readings of 162 systolic, 100 diastolic. Pulsation in the arteries of the right foot was easily felt, on the left side, the dorsalis pedis pulse was just perceptible and the posterior tibial doubtful. The left foot was slightly cedematous, a black scab occupied the position of the great toe nail, and on the inner side of this was a small granulating area extending a little onto the lateral surface of the toe. It was in a healing condition. The surrounding skin was purple in colour but warm. Exposed in a room at 20.5° the left great toe was the warmest of all, its base being about 33°, or about 4° warmer than the remaining toes. A reactive hyperæmia test showed delayed reddening of the left leg only, the return of blood was late from the calf downwards, the great toe reddening last.

In numerous tests it was found that the pain could be provoked by transferring the foot from water at 25° to water at 35° to 40°, the pain was greater as the temperature was higher, 40° gave severe pain if the immersion was continued, the pain was of the type familiar to him and occurred as usual in the great toe. When the foot was transferred from water at 25° to water at 40°, the pain usually began in 15, 20 or 30 seconds, grew in intensity

until at 1 to 1½ minutes it was so severe that relief was required and obtained promptly (in a few seconds) by reimmersing the foot at 25°. The pain caused by heating came in much the same time, reached much the same severity and subsided when the foot was cooled, whether the circulation to the limb was arrested or free. Dependency or elevation of the limb during the immersion tests failed to show any decisive difference.

A lumbar sympathectomy was followed by relief from pain for a little more than two weeks, pain then recurred in exactly the same form, situation, and severity.

Comment The burning pain experienced in the toe of this patient with senile arteritis is interpreted as resulting from its inflamed state. The tissues were in a susceptible condition, but the delay in the appearance of the pain on immersing the affected part in warm water, suggests that the nerves involved in the reaction were more deeply seated than usual.

CASE 8 Burning pain in left foot, with evidence of early thromboangitis obliterans

E. G., a housewife, of 52 years, had been under observation for several years for pain in the left foot, present altogether for 10 years. The pain started relatively abruptly in an attack in which the foot became deep purple and swollen. The pain ultimately became chronic, it was most noticed in the hot days of summer and then occurred each day within about one hour of rising and walking about. It would become steadily worse till evening. Going to bed relieved it, it disappeared in one or two hours. It was a continuous burning, sometimes throbbing when very bad, it would begin in the dorsum of the foot over the bases of the toes and would spread up the leg.

On examination the left foot was always found to be a little more highly coloured than the right, both feet, but especially the left, became more coloured when dependent. Both feet were habitually cool or cold. The left foot was always colder than the right from the region of the instep to the toes, the left great toe being usually only a degree or two above room temperature. Friction applied to the dorsum of this foot, to the front part of the sole and to its outer edge, elicited pain, the skin was not tender. The veins of the left foot were less prominent than those of the right, especially when both feet were warmed by immersion. The dorsalis pedis pulsation was full on both sides, but only the right posterior tibial pulse could be felt clearly. A reactive hyperæmia test showed manifest delay of the flush in the toes of the left foot. Resisted flexion movements of the foot gave pain in the left calf, but none in the right. The case was probably one of thromboangitis obliterans.

When the foot was transferred from water at 30° to 40° burning pain was felt over the toes, at first this was considerable, but it decreased and vanished in 4 min, the foot being dependent. The pain was described as

resembling her usual pain. Burning pain was quickly elicited (in a few seconds) by applying the copper cylinder at 40° or at 0° to the more susceptible areas of the foot. If a bath at 38° was used and a pressure of 70 mm Hg had been thrown onto the veins, a pain similar to that usually experienced was felt in the foot, and this was rapidly relieved by releasing the venous congestion. If, when the pain was present in the congested limb, a pneumatic counter pressure of 70 mm was thrown onto the front part of the foot, the pain was at once relieved, to return in about a half minute if the counter pressure was removed. These observations were many times repeated with the same result and are consistent with those described in other cases. In this patient, however, the burning pain following rubbing of the tender areas of the foot continued without break from the time of the rubbing for a period of about 1 min and this time could not be prolonged appreciably by arresting the circulation to the leg. It is mainly because the pain behaved unexpectedly and exceptionally in this respect that the case is included.

General comment

It has been shown that the skin, and it has been suggested that the underlying tissues, may present a condition termed conveniently the "susceptible state," a state in which burning pain is readily produced by warmth, by friction, and, in the case of the foot especially, by dependency of the limb. As has been described in a previous paper this state can be produced by damaging the normal skin in a variety of ways enumerated. As has been shown in this paper a similar condition of the skin is found in a number of distinct pathological conditions or diseases, the cases here recorded do not fully illustrate the conditions in which similar reactions of the skin have been observed, they are found for example in septic infections of the skin and in erythema nodosum. Because of the circumstances in which it arises, because it is often accompanied by redness of the skin and often by swelling, this susceptible state is known usually to be associated, or suspected to be associated, with local inflammation. It is of theoretical, and of no less practical, importance that this peculiar state of the skin should be recognised, and that the group of symptoms to which it gives rise should come to be regarded as a syndrome characterising a definite form of local disturbance of the skin, and one that is not peculiar to the skin of the limbs but may be found in other parts such as the face or chest.

VASODILATATION IN THE EXTREMITIES AND "ERYTHROMELALGIA"

The term "erythromelalgia" introduced to us by Weir Mitchell (11) has never in fact received precise definition, we rely upon general descriptions or loose definitions drawn by inference from case records. This lack of precision to some extent disarms criticism and makes the task of rearranging our knowledge in a new perspective more difficult. It will probably be considered reasonable to state that erythromelalgia has come to be regarded generally as a disease found in one or more limbs, and one in which attacks

of burning pain are induced by warmth or dependency of limb, and are accompanied by evidence of vasodilatation. Now the symptom burning pain occurring in just these circumstances has been dealt with in the preceding pages and in an earlier article, and we have been brought to the conclusion that such is to be regarded as significant of a local state of the skin and not of a given disease. This demonstration will be found in itself seriously to undermine any value the term *erythromelalgia* may have been thought to possess. In reading the records of cases published in the past under this diagnostic term and including with these the reports of cases by Mitchell himself, it is to-day quite obvious that a number of distinct diseases have been confused in one diagnostic category, and this has happened largely because they all present skin (or other superficial tissue) in what has here been called the susceptible state. One of the most notable instances of this confusion is illustrated by the disease *thrombo-angiitis obliterans*, there is no doubt that many cases of this malady and of other forms of arterial disease have not only passed unrecognised for what they are, but have been included under the term *erythromelalgia* (13, 14 and 15). It is evident from this and from other instances that when a patient has complained of burning pain in a foot or feet and especially when this pain has been provoked by hanging the limb down or in association with warmth of the skin the observer has been strongly impelled towards affixing the label of *erythromelalgia*, if redness of skin is present simultaneously, and especially redness that deepens with dependency of the limb then this more complex association is almost universally regarded as justifying the use of the term. It will be clear, however, from what has gone before that burning pain in the limb even if induced in the well defined circumstance postulated, cannot be regarded as a peculiar manifestation of one disease. The full combination of symptoms, including redness, occurs when the skin is in what has been termed the susceptible state, and the relevant symptoms, therefore, of nearly all the patients reported to be suffering from *erythromelalgia* in the past, can be interpreted quite reasonably upon this new basis, namely, a peculiar state of the skin that is held in common by a number of distinct diseases. It has further been shown that this condition is not confined to the skin of the limbs, but may affect that covering other parts of the body and even mucous membrane. The instance "*erythromelalgia*" is an interesting and important illustration of the difficulties, which can arise out of the attempt to identify a hitherto undescribed disease upon the basis of a group of symptoms, the method is sometimes unavoidable and when successful helps progress, but when it fails it may impede progress. I believe it to be in the interests of progress that the term "*erythromelalgia*," or painful redness of the limbs, should disappear as a term used to designate a disease, though it might be convenient to use the modified term "*erythralgia*" simply to designate the condition of painful redness exhibited by skin, whether it is found in the skin of the limbs or elsewhere. Each case presenting this syndrome should be dealt with upon its own merits. It is especially important from the

practical point of view that they should not be placed in a single diagnostic category, the same attitude is equally important from the standpoint of investigation, once this investigation probes more deeply than the immediate causes of pain, and begins to explore the reason why the skin is susceptible

In considering the term "erythromelalgia" there still remains to discuss the substantial question of associated vasodilatation, upon which in the past so much stress has been laid, it is necessary to enquire into the nature of vascular changes accompanying attacks of pain, and into their relation to this pain. For it is upon the basis of vascular manifestations that the loose idea has arisen and grown that "erythromelalgia", so-called, is a disorder of "vasomotor" origin.

There are several distinct questions to answer, and they have not yet been answered separately but have been confused. Are the periods of pain accompanied by vasodilatation, and if so is this vasodilatation an abnormal one? When pain and vasodilatation occur together, are they integral parts of some form of nerve storm, or does one cause the other? Lastly, is there any evidence that, in the cases considered, dependency causes vasodilatation in a limb? These questions will be discussed, but, before attempting to do so, it is necessary, owing to the manner in which discussion has proceeded in the past, to define the term vasodilatation and to consider what evidence can justify us in concluding that it is present.

Evidences of vasodilatation

The term vasodilatation can hold only one useful meaning in the present connection, namely, increase in the diameter of the vessels such as will induce an increased bloodflow to the territory affected. I am conscious in so defining it of departing from the strict meaning of the word, but believe it to be consistent with ordinary usage in this country. At all events I shall use the word strictly in this sense.

Reddening of the feet on dependency The idea that a simple increase in the depth of colour (blood colour) of the skin proves vasodilatation in the sense defined is of course erroneous. When the feet are allowed to hang down the pressure increases considerably within the vessels responsible for the vascular coloration of the skin, these increase in size, and the colour of the skin appreciably deepens. This is quite distinctly so even when the skin of the feet is normal, it is conspicuously so when the minute vessels of the skin have been damaged and lack normal physiological tone. The state of these minute vessels in skin that has been damaged by freezing, ultraviolet light, and similar causes has been studied closely, and their relatively toneless and irresponsive condition recognised (4). Sufficient here to say that if the dorsum of the foot is reddened by ultraviolet light or by the application of such a substance as mustard oil, the phenomenon of reddening of the foot on passing from the elevated to the dependent position is conspicuously displayed. Such reddening, immediately reversible as it is,

is interpretable as a purely passive effect and may not be used in evidence of an active change, yet this postural change in colour has been the most frequent evidence given for vasodilatation from the time of Weir Mitchell to the present day.

Sometimes, as in Mitchell's early reports, not only the engorgement of the foot but its assumption of a rosy colour on hanging it down has been emphasised. This also is inadequate evidence of increased bloodflow, if the minute vessels of the skin lack tone, and the foot is cool or cold when it is hung down, then bright redness of the skin may be expected to develop in the first instance, for the minute vessels fill from the arterial side, this colour gradually gives place to a more purple tint as the blood, newly entered but moving very slowly, gives up an abnormal percentage of its oxygen.

Swelling of the veins. Like the minute veins, the visible veins swell under hydrostatic pressure and their size as seen in the dependent feet is controlled chiefly by this pressure and by the temperature of the veins at the moment. In the cold foot the veins of normal people swell a little, in the warm foot they swell greatly on assuming the erect posture provided that the limb is allowed to hang flaccid, as it usually does when it is tender or painful. Swelling of the veins, though so often cited is inadequate evidence that vessels on the arterial side have dilated.

Throbbing, and unusually high temperature, of the foot. These two phenomena and especially the latter, afford the most convincing evidence of vasodilatation that we possess, and only statements of this kind can be relied upon in past records with any real degree of safety as showing the bloodflow to the tissues to have been considerable. Even so, caution must be exercised to eliminate numerous statements that refer to subjective sensations or which fail to discriminate these from what is felt by the observer. When a case report relates that the foot became burning hot in an attack, we may not conclude from this statement that it rose in temperature, for this is a form of description often used by patients to describe a painful sensation. Actual temperature readings are the most reliable of any evidence.

It is to evidence of throbbing or of heat, and to this only, that I shall refer in the following paragraphs.

Pain and vasodilatation

There is ample evidence in the records of cases reported as "erythromelalgia" to show that in attacks of pain the affected part is usually found to be warm or hot, and occasionally it is stated that the arteries of the affected foot throbbed, (Vulpian (18), Mitchell (11), Sturge (17), Collier (2), Brown (1) and many others). There is thus good reason to believe that the attack of pain may be associated with an abundant flow of blood to the part, there is much intrinsic evidence also that this flow is often far greater in the periods of suffering than during the periods of freedom from pain, the limb then being described as cooler or as actually cold. Brown in quite recent

observations has noticed that pain is associated with temperatures of the feet about the level of 33° , indicating a corresponding rapidity of bloodflow. But there is little or nothing in the past records to indicate that the temperature of the part was greater than was natural to the circumstances in which it was observed, or that there was therefore at the time what might be called abnormal vasodilatation.

It is clear that the true relation between pain and the temperature of the affected part has escaped notice hitherto. There is no evidence which shows, or really suggests that, in what is called "an attack," an abnormal event happens in the nervous system, central or peripheral, and causes an unusual discharge of vasodilator (or an unusual inhibition of vasoconstrictor) impulses on the one hand or of sensory (painful) impulses on the other. The relation between pain and increase of bloodflow is a different one, and has been made manifest in the observations of this communication and that which introduced it (8). The pain is preceded and is induced by rise of temperature. The skin is in an abnormal condition in which it is susceptible to certain temperatures, a rise of bloodflow, independently of the manner in which it is brought about, suffices to bring the temperature to the requisite point and thus to induce pain. The pain is at once induced by exposure of the limb to radiant heat or by simple immersion of the limb in water at the requisite temperature, and this will happen if the circulation to the limb has previously been arrested, it happens if the heat applied is limited to a small area of affected skin, but the pain is then quite local. Here there can be no question of vasodilatation being concerned.

Pain brought on in a warm bed is due in part to the direct warming of the foot and in part to an indirect warming owing to the general and normal relaxation of the blood vessels, pain occurring when a patient enters a warm examination room from colder surroundings is due to the natural vasodilatation, which ordinarily occurs in response to such exposure. Pain on walking a distance (as in Case 3) is due in part to the increased bloodflow and rise of temperature, which is a physiological reaction in the feet during that activity, but the occurrence of pain may be aided by mechanical stimulation of the foot (friction, etc.) and by its dependent position to greater or lesser extents.

When the normal relation of pain to temperature in susceptible skin is fully comprehended, a critical review of past records discovers no observations relating to vasodilatation that are not interpretable reasonably along such simple lines as these, and to the exclusion of abnormal reactions of the vasomotor system. It is natural enough to find the limb hot when it is painful, and even for the pulsation of its arteries to be increased, since warmth of the foot induces pain and brings the foot in this state to be examined. There is some evidence that, when tissues of the feet are abnormal, the vessels of these tissues may on occasion dilate more readily than is normal, it is possible that this happens in response to friction and to

walking on them, but this has not been shown conclusively, and, on the theoretical side, there is no present need to postulate it

There remains to discuss more closely the idea that attacks of vasodilatation are brought about by hanging a limb down, this idea has long been held and has played a prominent part in past writings

The effects of hanging the foot down

Mitchell stated (12, p 207) that whereas in "erythromelalgia" the temperature of the foot is apt to rise when this is dependent, that of the normal foot falls. It is right to add that he thought that in some patients, perhaps in all when the disorder has lasted long there is a fall and not a rise of temperature. He and his assistants used a surface thermometer, kept in contact with the skin of the foot for 10 minutes in the horizontal and in the upright posture, he concludes that the temperature of the dorsum and sole of the foot, in the normal subject, is in the average 0.4 to 1.0°C less when standing than when lying. In some of the observations the comparison was between the foot resting on a couch or hanging over its edge

Normal foot On very carefully repeating these observations, using thermal junctions, which respond rapidly to temperature change, they are found to have little value, the movement of surface temperature is a small one and it may consist of a rise or fall when the foot is lowered. The chief changes of temperature that occur in observations in which the feet are exposed freely to the air of the room are due to the draught caused by moving the feet from one position to the other which causes a fall of temperature, and to differences in the air temperature of the room at different levels, differences which are often conspicuous and may be in either direction. To overcome these and other errors the subject has been placed, lightly but warmly clad, lying on a special couch, which revolves on an axis from the horizontal to a vertical or to any intermediate position, the feet are boxed in so that a volume of air measuring about 1 cubic foot is carried with the feet from one position to the other. To maintain this air at a sufficiently constant temperature, a few small ventilation holes are cut in the box, which is fitted snugly but without pressure around the legs above the ankles. The testing thermal junctions are fastened to the feet and are connected by leads passing out from the box to the registering apparatus. Numerous tests have been made with full precautions upon a number of normal subjects, the temperatures of the room have been about 20° , and of the air in the box about 21° or 25° . It has been found to be very necessary that the subject should be resting and undisturbed by conversation or by movements of people about the room, for disturbances of these kinds produce changes of general vasomotor tone and consequent changes of skin temperature from time to time. But if proper precautions are taken, the temperature of the air surrounding the feet changing by no more than 0.1 or

0.2° over periods of an hour or more, then it is found that such changes of skin temperature as occur in passing from horizontal to vertical position and back again at intervals of 10 minutes are too small and too inconstant in degree and in direction to possess any significance from the present point of view

Stewart (16) encased the feet of a normal subject in a special calorimeter and measured the heat elimination from the feet when the subject lay supine or sat. Although he says that the blood flow to the foot seems to be somewhat greater when the legs hang down, his observations were too few to warrant a definite conclusion. In numerous observations upon six normal subjects we have employed Stewart's apparatus,* the feet remaining in the stationary calorimeters while the subject moved from lying to sitting, or lying to standing positions, or *vice versa*, with as little disturbance as possible. The calorimeter temperatures used were 29.5° to 32.0° and the room temperatures 21° to 25°, the subjects were lightly but warmly clad. When lying and sitting are compared changes in heat elimination are absent, or slight and inconstant in direction. When lying and standing are compared, then heat elimination is a little reduced in the latter posture, probably because the circulation to the soles of the feet is obstructed when the weight of the body falls upon them.

Abnormal foot. The observations upon normal subjects were carried out at some length, in the hope that when cases suffering from so-called "erythromelalgia" came similarly to be investigated, a clear comparison might be made and a contrast established. Early in the investigations, however, it became evident that the usual phenomenon of flushing on dependency in patients has been misinterpreted, it is not a vasomotor, but a passive effect, as previously explained. Actually no case has been encountered in which flushing of the feet on dependency has been accompanied by a rise of skin temperature except occasionally and fortuitously (Case 2). The evidence of previous records must, however, be briefly reviewed from this standpoint.

We owe to Mitchell (11) the traditional description — "When flushing is a part of the phenomena of this interesting malady, it comes on during the erect posture slowly in milder cases, and almost at once in others, and involves both veins and arteries. The foot gets redder and redder, the veins stand out in a few moments as if a ligature had been tied around the limb, and the arteries throb violently for a time, until at length the extremity becomes of a dark-purplish tint. In the worst cases, when the patient is at rest, the limbs are cold, and even pale. The flushing, which, at first, seems to be an active condition, accompanied with rise of temperature, in a few minutes becomes passive, that is, the arteries cease to throb, the heat lessens." This is his graphic description of 1878, but when we turn to his contemporary case reports, confident of finding in these the justification of his general account, we are strangely disappointed. His general description, so often repeated

* In these observations I enjoyed the assistance of Dr. W. Hess.

by others almost in his words, is far from being substantiated in its reference to the essentials, namely, throbbing arteries and heat, it relies upon a meagre account of a case by Vulpian (18) and upon Mitchell's personal account of a sailor (his Case 1) who was examined after walking for an hour, and found to have swollen congested feet, in which the arteries throbbed Lannois (3) writing two years later, repeating Mitchell's description and being persuaded of the vasomotor origin of the malady, brought in support a single case, he said that the upright position accentuated the symptoms and raised the temperature of the foot but although he gave many readings of temperature, there is no observation amongst them to confirm this last statement Mitchell in citing a case (Case LVIII) in his book (1897) refers to a rapid augmentation in the force of the arterial pulsation when the foot hung down, "a true vascular storm", but he took many measurements of skin temperature from this patient and found this fell when the feet were pendent It is highly significant that Mitchell failed to comment upon this obvious discrepancy In another case (Case LIX) he found temperature readings higher by 0.2 to 0.6° in the perpendicular as compared with the horizontal position, values similar to and in the same direction as those found by Collier (2) in the report of his Case I Such differences are in fact without significance, being within the error of measurement by the methods used In Collier's statement that the cold foot of his patient became very hot to touch when hung down and in Mitchell's inference that he could induce throbbing regularly in a foot (Case LVI) by asking the patient to hang it down,* we come nearest to grounds for suspecting that there may be very occasional cases in which dependency brings increased bloodflow to the affected limb We search in vain, however, for what is required to convince, namely, a deliberate statement that throbbing of arteries or a significant rise of temperature was observed to occur regularly whenever the limb was hung down Flushing of the foot, swelling of the veins, and pain have been shown during the present observations to appear when the foot is hung down, while the corresponding temperature readings have indicated that there has been no increase in the bloodflow to the limb It is quite clear, therefore, that if it is correct to speak of these symptoms as "an attack" induced by dependency of the limb, vasodilatation cannot be regarded as an essential part of it I think that the occurrence of increased bloodflow resulting from posture is a misconception, arising first in Mitchell's mind owing to his misinterpretation of the significance of passive flushing of the skin, and that his reiterated statement and the weight of his authority have led subsequent observers to the support of his view by casual observations, which, had they been properly repeated and controlled, would have been interpreted differently and in a manner already indicated However, in

* Later enquiry, however, leads me to understand that Mitchell did not demonstrate this patient in the manner described in his book, which was arranged in lecture form for literary reasons Thus being the position, the inference that the phenomenon could be induced regularly in this case may not be drawn

summing up, it may be safer to say that increased bloodflow occurring in these cases as a reaction to dependency of the limb is at present unproved and can at most occur in very exceptional cases

Whether we regard this clause of reservation as necessary to provide for very exceptional cases or not, it is clear from the observational work of the present paper that dependency does not produce its effects ordinarily in this way, but that pain comes through an increase in the tension of the tissues, consequent on the hydrostatic rise of vascular tension within them *

Thus the original questions (page 197) relating to vasodilatation are to be answered as follows Pain may be accompanied by vasodilatation but also occurs without it There is as yet no evidence that vasodilatation such as may be found to accompany pain is an abnormal vasodilatation for the circumstances in which it occurs At this point, however, it is to be noted that there is a suggestion that vessels in a susceptible area may be a little more than usually disposed to dilate to vasomotor and other influences, an abnormality of local response, be it observed, and not one of the vasomotor system Vasodilatation is not an integral part of the attack, pain is caused by increased temperature and this may be brought about by physiological increases in bloodflow or in other ways Lastly, there is no evidence that increased bloodflow is caused in a limb by hanging it down, there is evidence that pain so arising is provoked by hydrostatic tension in the vessels

PAIN IN RAYNAUD'S DISEASE

CASE 9 *Raynaud's disease, burning pain in fingers during recovery from attacks*

W G, a factory hand of 50 years, was seen in December, 1930, and related that for a period of six years his fingers had frequently become blue, cold and numb when exposed in cold weather, or when washing in cold water The five fingers of each hand were affected in this way The fingers would become blue at their tips at first, the discoloration spreading up and ultimately invading the hand as high as the wrist The feet were less affected, and the face unaffected Sore places appeared on each of his fingers from time to time and the nails of each of his fingers had been lost, but had regrown

On examination the fingers were cold, a little swollen, and of a colour a little deeper than normal All the finger tips presented small depressed scars, least conspicuous in the case of the thumbs, the nails were short and rough On the tips of the 3rd and 5th left fingers were two small indolent but healing areas of necrosis The skin over the distal phalanges was

* The burning pain occurring on hanging a foot down is often preceded by an aching pain which the patient distinguishes and which perhaps proceeds from deeper tissues I have desired not to overload this paper by its consideration, but may here state that this pain seems also to be the result of hydrostatic vascular tension, as corresponding tests indicate

abnormally rigid and the corresponding joints could not be flexed fully. Immersion of a hand at 15° for 12 minutes caused all the fingers to become deeply cyanotic, immersion at 32° then led to very slow recovery, succeeding parts of the fingers becoming bright red in colour over a period of 10 minutes.

The man's chief complaint was of pain in the fingers during recovery from their attacks of discoloration. The pain was stated to be under the nails, burning in quality, severe, usually uniform in intensity, but occasionally throbbing. It would last for several minutes.

If an attack of discoloration was induced by immersing the left hand in cold water (15°), and this hand was transferred to water at 35° , distinct burning pain lasting several minutes was experienced in the 3rd and 5th, the inflamed, fingers. The pain was described as precisely similar to that experienced in ordinary attacks. It was due, however, not to return of bloodflow to the fingers, but to rise in their temperature. The pain was experienced if the circulation was shut off to the hand before rewarming it, and if the circulatory arrest were maintained the pain would pass away in a few minutes. Release of the circulation when the pain had passed away brought no recurrence, and no pain occurred after restoring the circulation to the hand maintained warm throughout circulatory obstruction. The pain was induced only in the 3rd and 5th fingers, those presenting small unhealed necrosed areas. Similar pain was induced by cooling and subsequently warming the 3rd finger by itself. If the water used to rewarm the finger was at 38° , the pain was of increased severity and, if the circulation was not cut off during the observation, throbbing was added. When water at 40° was used, the burning pain was sufficiently intense to make the man sob, the pain was less intense if the circulation was stopped to the finger during the rewarming. The pain lasted 2 to 5 minutes, disappearing gradually, reimmersion in cold water always brought comparatively quick relief.

Comment and observation upon similar pain induced in normal fingers. The observations recorded show that severe pain in Raynaud's disease may result when the circulation to the fingers becomes restored after an attack of discoloration, the cold fingers rising in temperature as warm blood enters them. This phenomenon was observed in our patient only in fingers that were still inflamed. It is not to be inferred that the pain described is the only form to which patients with Raynaud's disease are prone, though it is almost certainly one of the chief forms, and perhaps the only severe form, of pain experienced. Moreover, it is not to be inferred that a previously inflamed state of the finger is necessary, though, as this patient illustrates, it predisposes to the painful reaction.

Similar pain can be induced in the fingers of normal subjects by using colder water. If the finger of a normal person is immersed for 5 minutes in ice-cold water with the circulation cut off to ensure adequate cooling, and it is then transferred to a bath at 36° to 38° and the circulation released,

pain starts in about 15 or 20 seconds. It is a burning pain, varying in degree in different subjects, but sometimes so severe as to be well-nigh intolerable. It is felt under the nail, in the pulp of the finger, or more diffusely over the end of the finger, it continues unchanged, or may throb with the pulse, and declines, having lasted 1, 2, or more minutes. This pain seems to be identical with, though it is induced less easily than, that experienced in Raynaud's disease, as in the patient, it is experienced, though less intensely, if the finger is transferred from cold to warm water without releasing the circulation to it, and when present it is quickly relieved by re-immersing

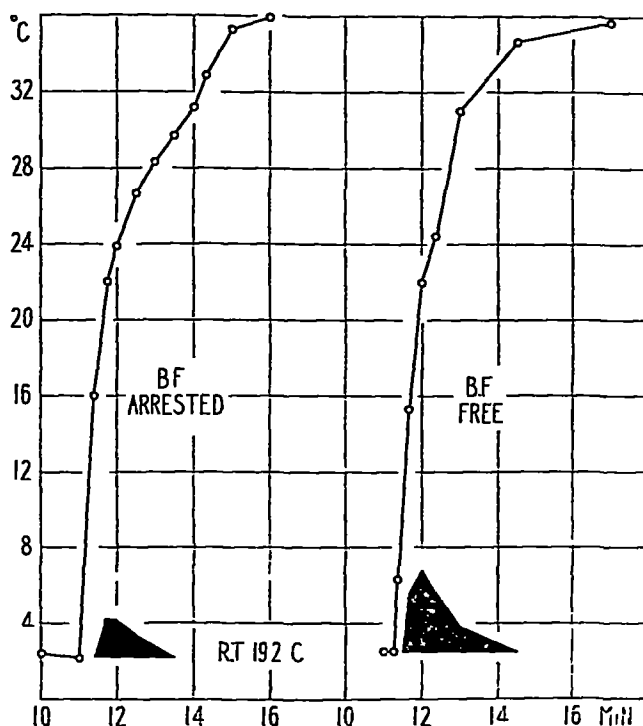


Fig 1 Chart of temperature readings taken by means of a thermal junction fixed and covered by strapping to the skin behind a finger nail. The curve of temperature is the result of transferring the finger from ice cold water to water at 37°. The black figure illustrates pain indicating its time of onset and offset, and the relative intensities. Two observations are illustrated, one with the bloodflow to the arm free and the other with arrested bloodflow.

the finger in iced water. In a number of instances the rate at which the temperature of the skin at the base of the nail rises has been charted in relation to this pain. The charts (Fig 1) display the rise of surface temperature, and it should be remembered that the effective temperatures are perhaps those of deeper parts. Charts such as these emphasise the relation

of pain to a steep gradient of rising temperature. The pain often subsides and disappears as shown in Fig. 1 while the temperature of the finger is still rising. The facts suggest a mechanism similar to that previously discussed. We have insufficient evidence safely to formulate a hypothesis in detail. There is only enough to warrant our discussing the pain in a preliminary way. It seems inadequate to regard the steep rise of temperature as causing pain by its direct physical effect, for the finger that has been cooled and warmed and has recovered from pain is often hypersensitive to warmth (10°) subsequently, and it remains tender to friction often for hours. It is difficult to avoid concluding that excessive cooling of the finger has damaged its tissue. Another reason for the same belief is that if the finger is maintained in the ice-cold bath for 10 min. the pain on rewarming with the circulation still arrested is much more intense, and lasts very much longer, than if the cooling lasts for 5 minutes only, yet the degree of coldness reached must be almost if not quite the same and so must the steepness of the rise of temperature in rewarming, here the length of cooling seems to matter. The pain often lasts so long in the first case (3 or 4 min.) as to suggest that a released substance is held up by the circulatory arrest in adequate concentration to produce continued pain in these circumstances. There are minor difficulties, however, in the way of this conclusion. There is nothing very heterodox in the idea that intense cold, as distinct from freezing can produce the necessary damage to occasion the release of the substances from the cells. The same idea has arisen from distinct lines of observation and argument on several occasions. Thus supercooled skin that has not frozen may wheel subsequently (9). Another instance is the customary vascular response which follows less severe but prolonged cooling, which has been ascribed to release of a histamine like substance (6).

The pain here described, though similar in certain respects to that provoked in superficial lesions of normal skin, as by ultra-violet light, follows immersion in warm water after a much longer latent period (usually 20 to 30 as compared with 2 or 3 sec.), this delay possibly means simply that the pain is derived from deeper structures and not from the skin. In the normal subject its localisation at the ends of the fingers is not to be ascribed to the more rapid re-warming of these parts owing to their rich content of arteriovenous anastomoses, since the localisation is the same when pain occurs in a finger to which the circulation is obstructed. It is presumably due to some peculiarity, such as the supply of nerves, in the anatomy of the pulp of the finger and nail bed.

While the suggestion here made as to the origin of pain must be regarded as very tentative, the observations are perhaps not without interest in that they may help us to understand the pain in the fingers of Raynaud's disease, in which the inflamed condition of the finger tips may be regarded as predisposing to the easy production of pain.

DIFFERENTIATING FORMS OF TENDERNESS

To be able to differentiate clinically between tenderness (or soreness) of the skin when this results from the skin's own susceptibility, and tenderness resulting from lesions of the central nervous system or of the peripheral nerves, would obviously be important. From a limited experience of cutaneous tenderness in peripheral neuritis it would seem that this can now be done by simple tests. Skin in the susceptible state is stimulated unusually by warmth (40°), the tender skin in neuritis does not seem to be unusually affected by it. If skin in the susceptible state is rubbed or stretched it becomes painful, this pain subsides and gives place to long continued burning pain after an interval. The tender skin in neuritis responds to stimulation painfully, but this pain seems to end at once, or almost at once, with the ending of the physical stimulus. It is suggested that these tests may ultimately be found reliable in differentiating the two forms of hypersensitivity, that they are valuable I can state from personal experience, but they must be explored further before they can be used generally and with confidence.

GENERAL NOTE ON PAIN

In considering the nature of pain, it may be said that much is known already about the forms of interference capable of inducing it, and about the peripheral nervous paths conveying pain sensations to the central nervous system. Much less is known about the manner in which the original interference excites the nerve endings, but this study has begun. The following ideas are put forward, not as final conclusions from the studies of this and the previous paper (8), but rather as a basis for further discussion and enquiry, for it is already obvious that there is here a field of fruitful and interesting work.

When we consider the mechanism concerned in exciting the pain nerve endings, it would now seem necessary from this standpoint to divide pain into two distinct types.

There is pain of the first order, which is produced by physical agencies such as the brief application of heat, or by the exercise of tension. Pain of this order can often be recognised by the shortness of the latent period, which intervenes between the application of the stimulus and the onset of pain, and by the rapid subsidence of pain when the original stimulus is withdrawn. Between what we call the stimulus, in such instances, and the actual excitation of the pain nerves there may be intermediate physical or physico-chemical processes, it is even possible that in some of these cases stimulation is direct and in some cases indirect, a difference that would require a further and corresponding subdivision of pain, but if such intermediate processes do exist in instances of pain belonging to this first group then these must be rapidly reversible with the withdrawal of the stimulus. In normal circumstances pain of the first order is experienced when the

physical stimulus, such as heat or tension, is unusually intense, but pain of the same order may be produced by physical stimuli ordinarily below threshold value, if the appropriate nerves have undergone preparation, and thereby have become unusually sensitive to stimulation. The pain following at once, or almost so, when superficial tissues are punctured, incised, crushed, burnt, or severely stretched clearly belong to this first order. Similar but non-injurious stimuli, ordinarily below threshold value, are effective in inducing pain from tissues that are tender. Transient pain arises from such tissues when they are touched, warmed, or manipulated gently. Such pains must also be regarded as belonging to the first order. Most pains concerned with increased tension, pain developing in a dependent limb, or pain which comes in throbs with the pulse (as in disease of dental pulp, or in cutaneous abscesses, or in certain forms of headache) can almost certainly all be regarded as belonging to the first order, and others such as that developed during the single strong or long continued contraction of muscle, somatic or visceral, may reasonably be suspected to be of similar origin. Thus it is apparent that in attempting to classify pain, as this is experienced by patients, a very large number of different kinds of pain must be referred to this first grouping.

Pains of the second order are those that cannot be regarded as arising directly from the primary stimulus, but through a relatively stable intermediate process. Such pain has usually a more delayed onset, rising gradually to its summit, continuing for a period of minutes or longer without any appreciable change, and declining very slowly. Continuing without appreciable change, it may be termed a *smooth* pain an important quality to distinguish. Pain of this order may be recognised definitely if it can be shown that the period of continuous pain is prolonged, the decline of pain being deferred, by arresting the circulation to the part from which the pain is derived, for such an observation shows that the pain is dependent upon a chemical or physico-chemical state, which the original stimulus has set up and which is irreversible or stable in the absence of bloodflow to the part. The first pain of this class to be recognised was that arising in somatic muscle working without blood supply or with inadequate supply (10). Angina pectoris, whether arising spasmodically or as an immediate sequel to coronary thrombosis has almost certainly a similar origin, other examples will doubtless come to light. Such pain is due to a chemical or physico-chemical product of muscular work, accumulating during circulatory arrest, and dispersed when the circulation is restored. From our present standpoint the precise nature of this accumulation is unimportant, as between two of the more obvious possibilities, the accumulation of muscular metabolites and their subsequent removal by diffusion on the one hand, or by oxidation on the other, the second, in the light of recent evidence* seems the more probable.

* Unpublished observations by Pickering and Wayne

Other pains of the same general order have been studied in the present series of observations. They have been shown to arise in superficial tissues like the skin, as after-effects of injury, such as burning. They can also be provoked, in injured tissues that are tender but painless, by friction, by severe tension and perhaps in other ways (perhaps by raising tissue temperature), but the pain considered does not come at once under these influences, it arises after a lesser or greater period of delay, and then, characteristically, the pain waxes gradually and reaching its full value, continues for a long period (minutes or more) as a smooth pain, subsequently to decline very gradually. The chemical or physico-chemical basis of this pain is clearly different from that underlying the pain developed in the working but ischæmic muscle, for although both are prolonged by circulatory arrest, the muscle pain vanishes much the more rapidly when the circulation is restored. Clearly the two processes are different from each other, nevertheless in each case there is definite evidence of an intermediate process, standing between the original stimulus and the excitation of the nerve, the establishment of a chemical or physico-chemical state irreversible while the bloodflow to the part is in abeyance, it is to this that the time relations of the pains, which are probably characteristic, are to be attributed, and it is on this basis of evidence that the corresponding pains are placed together in one class, namely, in that of pain of the second order.

CHIEF CONCLUSIONS

1 "Erythromelalgia" is a term that should be abandoned as the name of a disease. The term "erythralgia," however, might be employed usefully to designate a peculiar condition of painful redness of the skin, which is common to a number of diseases.

2 This painful redness is due to a local condition of the skin, previously referred to as its "susceptible state", it is often, perhaps always, inflammatory. The skin of any part of the body, and mucous membrane, may be affected. The chief manifestations of patients displaying this condition in an extremity are as follows —

- (a) The skin of the extremity is reddened, and this reddening greatly deepens when the limb hangs down. The reddening of the skin is the result of a relatively toneless condition of the minute cutaneous vessels, and the deepening of colour on dependency is due to passive congestion and does not signify vasodilatation.
- (b) Burning pain is induced whenever the temperature of the skin rises to a certain level, normally insufficient to produce pain, and this is so whether the heat is brought by increased bloodflow or is applied from outside. The same pain may be induced by extreme cold, local friction, or by tension. When it comes during walking it is chiefly

the result of the warming up of the foot and of friction. When it occurs in a limb allowed to hang down, it is due to hydrostatic vascular tension. It is the simple relation of pain and temperature, which is largely responsible for the erroneous belief that "vasomotor storms" form an integral part of the condition from which these patients suffer. There is no evidence that in what are called "attacks" a disturbance occurs in the central nervous system, such as would give rise to an unusual discharge (or inhibition) of vasomotor impulses or of sensory impulses. It is suggested, however, that in tissues in the "susceptible state" vasodilatation may be brought about a little more readily, or more conspicuously, owing to the state of these tissues.

3. There is no evidence that there is any appreciable change in the bloodflow in the normal foot on changing it from a horizontal to a hanging down position. When the weight is placed on the foot in standing, the bloodflow to it seems to be a little decreased. Though reddening may occur, there is insufficient evidence that increased bloodflow to a limb can be brought on in pathological subjects by allowing the limb to hang down.

4. Severe burning pain of inflamed fingers in Raynaud's disease can be caused by the quick warming of fingers occasioned by a return of blood to them when they are cold. Normal fingers present the same phenomenon if the range of temperature change is sufficiently increased.

5. Burning pain in the skin may follow firm stroking of the skin in some cases of urticaria factitia, and the stroked skin is subsequently unusually susceptible to warmth.

6. Burning pain in all the circumstances discussed is considered to have a similar underlying basis, namely, the release from the damaged tissues of a natural substance, which acts on the pain nerve endings, lowers the threshold of these to tension, and to heat, causing them to discharge pain impulses at times even under ordinary conditions of temperature, etc.

7. Criteria are suggested for differentiating between tenderness of the skin having a local cause and that which is secondary to disease in the central nervous system or peripheral nerve trunks.

8. Considered from the standpoint of mechanism there seem to be two chief forms of pain. Pain of the first order begins and ends with the original physical stimulus to which it is possibly a direct response. Pain of the second order is more delayed in onset and often outlasts the original stimulus, this happens because a relatively stable intermediate process, chemical or physico-chemical, intervenes, and is responsible for the actual excitation of the nerve endings.

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VASODILATATION IN THE HANDS AND FEET IN RESPONSE TO WARMING THE BODY *

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ALTHOUGH the blood vessels of the feet have been less extensively studied than those of the hands, they appear to behave in a similar way. Thus, when the body is warmed, the vessels of both upper and lower extremities dilate (7), recently, however, we have noticed in studying patients suspected of peripheral vascular disease, that warming the body produces vasodilatation more easily and more consistently in the hands than in the feet. In this paper it will be shown that this is also true of normal subjects and its explanation will be discussed.

Method

Vasodilatation resulting from warming the body depends not on a reflex from the skin, but on the excitation of some central mechanism by the rise in temperature of the blood (9). The precise method used to raise body temperature is probably unimportant, two have been used.

In the majority of the observations here described the body temperature was raised by an immersion method, similar to that described by Gibbon and Landis (2). One forearm and the opposite leg of the recumbent subject were immersed in stirred water at 42-43°C, the other forearm, bared to the elbow, rested on a cork mat, while the other foot, bared to the ankle, lay on a firm pillow.

In a few observations the warm chamber (7) was used, the trunk of the sitting subject being enclosed, while the forearms from the elbows, and the feet from the ankles, remained exposed, both pairs of extremities resting on cork mats.

The vascular responses of the extremities were usually studied by means of skin temperature, measured from the back of the distal phalanges of the exposed digits and from other areas described later. The room temperature was recorded from a thermal junction in the air between the feet. In

* Work undertaken on behalf of the Medical Research Council

certain circumstances, Stewart's calorimeters (10, 11) and plethysmographs were used

The four subjects here investigated were healthy adult males under 30 years of age, the characteristics of their peripheral circulation were not unusual, except perhaps in the case of P whose extremities tended to be cooler than is usual

Results

Extremities cool In the first series of observations the feet and hands had been naturally cool for half an hour or more before the test was made. The feet were not uncovered until beginning the observation. After readings of skin temperature had been recorded for 10 or more minutes, the body temperature was raised.

The results are summarised in section A of Table I and illustrated by Fig 1. Table I shows that a rise of skin temperature starts in the fingers 3 to 13 minutes after beginning to warm the body, the rise follows its usual course, (7) being slow at first and later more rapid. In the toes the rise of temperature begins later than in the fingers and is at first much slower, thus a rate of 0.1° per min. is attained more quickly in the fingers than in the toes. This difference in the time of onset of vasodilatation in hands and feet was observed in all subjects. It was greatest in P in whom on one occasion in a room at 16°C the skin temperature of the toes failed to rise during 2 hours warming by the immersion method, in this observation the rectal temperature, measured by a standard mercury thermometer, rose from 36.85°C at the beginning to 37.6°C at the end, and sweating was profuse during the last hour. Another observation on the same subject is shown in Fig 1. The temperatures of fingers and toes were initially slightly below, and tended to follow, room temperature which rose slowly throughout. At the 10th minute the left arm and right foot were immersed in water at 43°C . At the 18th minute the skin temperature of the right index finger began to rise and, as always happens in normal subjects (7), soon reached a high level at which it remained. After the 76th minute the heel gradually became warmer, but the temperature of the toe did not begin to rise more steeply than that of the room until the 88th minute. This rise was much slower than that of the finger and at the 138th minute, when the observation was terminated, the toe temperature had reached only 29.8°C . The observations on the other subjects agree with this in showing a delayed onset of vasodilatation in the foot, but in the other subjects, the rate of rise of toe temperature from 23° upwards was much faster than in the example given, and proceeded ultimately to 32°C or more. This illustration has been used, however, because it shows that an apparently abnormal (incomplete) response may be obtained from the foot of a normal subject when the extremity is initially cold. In some subjects vasodilatation has begun in the heel later than in the toe.

TABLE I

To show the time, after beginning to warm the body at which a rise of skin temperature begins in the fingers and toes. In all observations except the first the body temperature was raised by immersing a forearm and a foot in water at 43°C

Subject	Date	R T °C	Initial temp		Rise begins		Rise† begins		Posture
			Fing	Toe	Fing	Toe	Fing	Toe	
			°C	°C	Min	Min	Min	Min	
Sect A									
P	22 8 32	20.0	20.8	19.9	3	17	3	23	Sitting
M	8 10 32	19.5	21.6	22.2	5	7	5	11	Sitting
P*	10 10 32	18.5	19.4	21.1	12	15	12	23	Lying
P	28 11 32	16.0	17.2	17.6	9	> 120	20	> 120	Lying
M	28 11 32	18.5	16.6	18.3	10	13	12	21	Lying
Ho	29 11 32	18.5	20.0	23.2	9	13	9	15	Lying
He	7 12 32	15.0	16.3	16.5	11	14	12	19	Lying
P**	19 4 33	18.0	17.8	18.0	8	40	14	60	Lying
M.	21 4 33	17.0	17.0	17.0	13	21	13	29	Lying
Sect B									
M.	15 3 33	20.5	30.6	28.8	2	4	2	5	Lying
	"	"	25.2	23.7	4	5	4	12	Lying
Ho	16 3 33	20.0	20.8	22.0	8	8	8	9	Lying
P†	19 4 33	19.0	23.8	23.7	8	14	8	14	Lying
M	21 4 33	18.0	27.2	25.5	6	14	6	16	Lying

* Foot in sock and shoe

† Illustrated in Fig 2

** Illustrated in Fig 1

‡ At rate of 0.1° per min

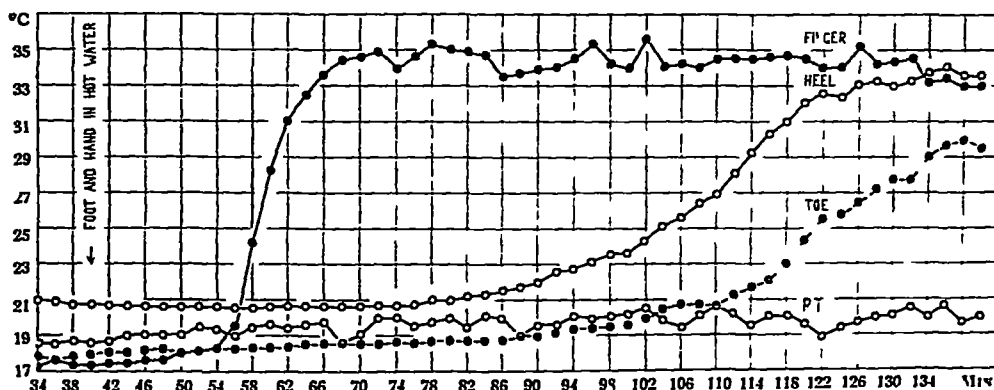


Fig 1 P April the 19th, 1933 Shows the temperature of the right index finger, the left great toe and the left heel of a horizontal subject whose extremities had been naturally cool for more than an hour previously. The right arm was exposed from the elbow the left foot from the ankle. At the 40th minute the left forearm and right foot were immersed in water at 43°C. In this and subsequent figures R T = room temperature

Extremities recently warmed To see whether vasodilatation also begins in the toes later than in the fingers when the extremities have been recently warmed a second series of observations was made

In these, which are summarised by section B of Table I and illustrated by Fig. 2, the clothed subject had been wrapped in blankets enclosing two hot water bottles for an hour or more before the observation was made. An arm and foot were then exposed and readings of their temperatures begun. As Fig. 2 shows, and as was always observed, the toes under these circumstances are about 1° cooler than the fingers, sweating was more profuse on the toes. After a preliminary observational period of 15 or more minutes the blankets were unwrapped and the hot water bottles removed. The fingers and toes began to cool simultaneously in all observations. When the digits reached about 25°C the body was rewarmed by the immersion method. Table I shows that under these conditions also the response of the toes usually begins a little later than that of the fingers, but the delay is rather less than when the extremities were initially cooler*. The rate of

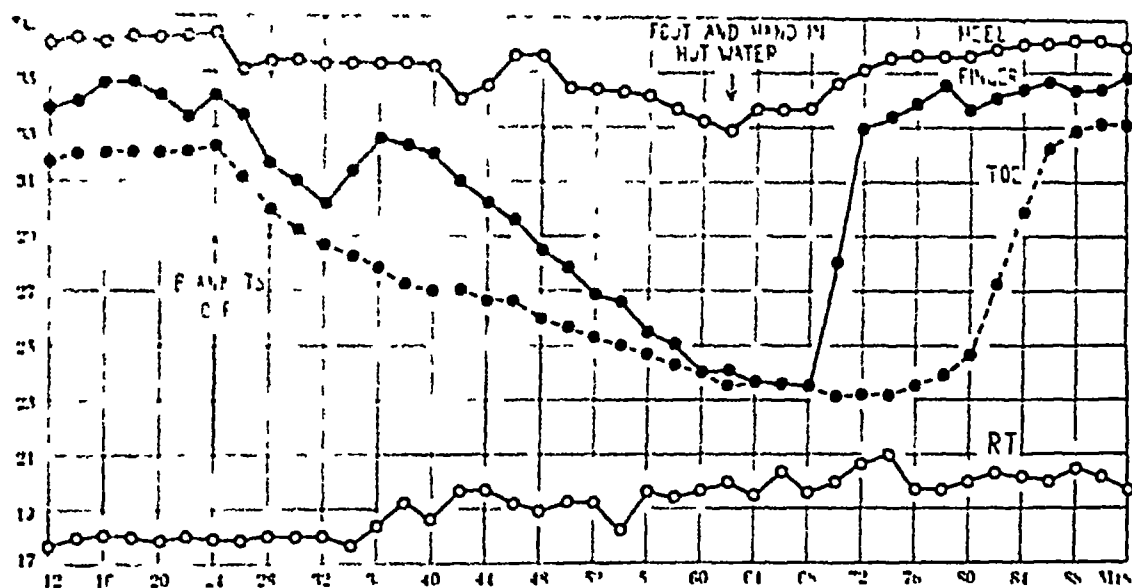


Fig. 2 P April the 19th, 1933 After the termination of the observation recorded in Fig. 1 the subject was wrapped in blankets with two hot water bottles on the trunk for 1 hour 48 min., when the right arm and left foot were exposed as before and skin temperatures recorded. At the 24th minute, the blankets were unwrapped and the hot bottles removed. At the 62nd minute the left forearm and right foot were immersed at 43°C .

rise of skin temperature over a range of $25-30^{\circ}\text{C}$ did not differ from that which was attained when the extremities were cooler, except in the case of P, who now falls into line with the other subjects. The observation on this subject recorded in Fig. 2 was made two hours after that recorded in Fig. 1. Fig. 2 shows that after warming the body a rise of skin temperature was evident first in the heel, which was warmest, then in the finger and last in

* Table I shows that, when the response started, the temperatures of the digits had reached as low a level in some observations of Section B as in some of Section A, the proximal portions of the extremities, which cool more slowly, were consistently warmer in Section B than in Section A.

the toe, in comparison with Fig 1, the rise in temperature of the toe is less delayed, more rapid and proceeds to a higher level. As already remarked, this subject is exceptional in showing a slow and incomplete response from the toe when the foot is initially cool, when the foot is initially warm, the toe responds in the same way as do those of other normal subjects.

The delay in vasodilatation of the toe is further reduced when the initial temperature of the extremities is higher and is finally abolished at body temperature. At such temperatures vasodilatation cannot easily be detected by measuring skin temperature and we have used Stewart's calorimeters (10, 11) and plethysmographs for the purpose, plethysmography is the only simple method available at body temperature.

When a hand and a foot are simultaneously immersed in Stewart's calorimeters containing water at 31 to 32°C, then the vasodilator response to immersing the other arm in water at 42 to 43° begins slightly but definitely later in the lower than in the upper extremity (Fig 3).

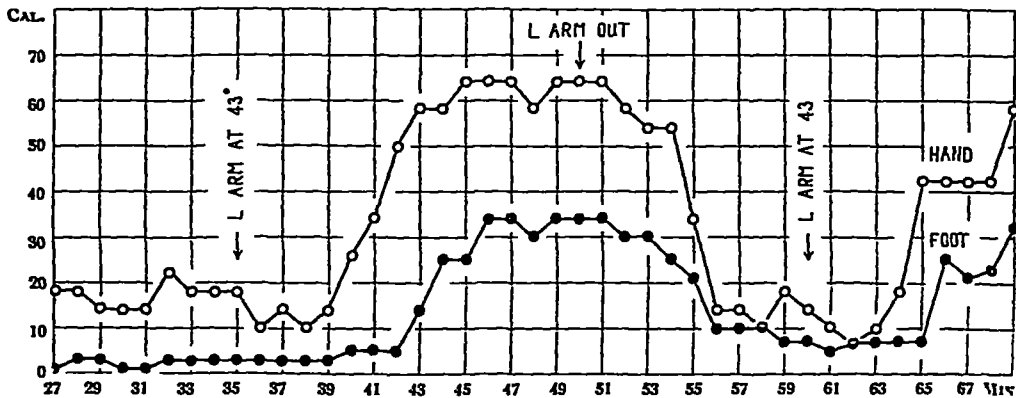


Fig 3 Ho October the 2nd, 1933 R T = 19.5°C Shows the heat elimination in calories per 100 cc of tissue from the right hand and right foot which after preliminary immersion in a bath at 32°C for 20 minutes were placed in Stewart's calorimeters containing water initially at 31.4 and 31.2°C, respectively. The left arm was immersed in water at 43°C at the 35th minute, removed and dried at the 50th minute, and reimmersed at the 60th minute.

Fig 4, which is representative, shows volume curves simultaneously recorded at 36°C from the forearm and leg of a normal subject. The two curves are nearly parallel, the rapid reflex vasoconstriction, due to the stimulus of heat applied to the skin, and the later and slower vasodilatation, arising from the central excitation produced by the return of warm blood from the immersed limb (9), begin simultaneously in upper and lower extremity. This observation confirms that made earlier by Müller (8) who, however, did not state the temperature of his plethysmographs.

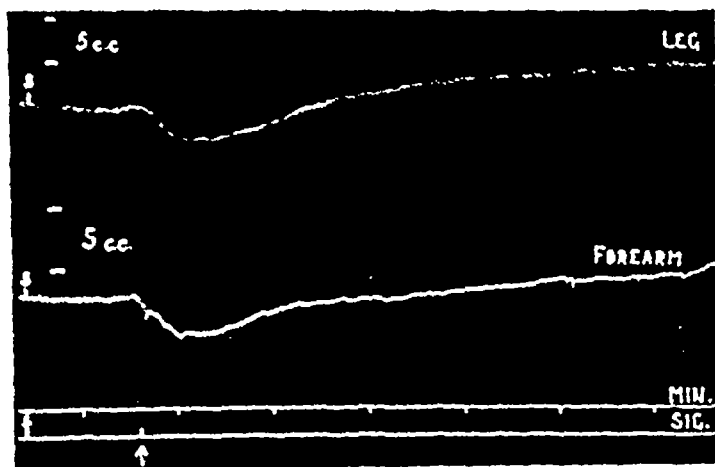


FIG. 1. K. O. October 24th 1937. RT. 20.5°C . Shows plethysmographic curves recorded simultaneously from the right forearm by the apparatus described by Lewis and Grant (6) and from the right leg and foot by the apparatus described by Drury and Jones (1). Simultaneous points in the curves are shown by the marks S. At the arrow the left forearm was immersed in stirred water at 47°C . Temperature of plethysmographs 36°C . Volume of leg, including foot, 1500 cc. Volume of forearm ≈ 700 cc.

Discussion

The plethysmographic curves just described show that when a forearm is immersed in hot water, changes in vasomotor tone of both reflex and central origin affect upper and lower limbs simultaneously and in a similar way. Again, we have seen (Fig. 2) that when the body is cooled, the skin temperatures of the warm upper and lower extremities begin to fall simultaneously. Thus it seems probable that alterations of temperature produce changes in vasomotor tone in upper and lower extremities of the same kind and at the same time. We may not suppose, therefore, that when the body is warmed, a delayed rise of skin temperature in the toes is due to a delayed change of vasomotor tone in the feet. Nor can the difference in behaviour of hands and feet be accounted for by a difference in vascularity, for such a difference, if it exists, would not explain the occasional absence of vasodilatation in the feet. The delay occurs when the extremities are exposed to temperatures below that of the body and its explanation requires knowledge of the effect of local cold on vasodilatation, to a consideration of this effect we now turn.

It has been shown by Lewis and Pickering (7) that when the body is warmed with the hands initially at different temperatures the onset of vasodilatation is delayed in the cool hand, an effect attributed to the local constrictor action of cold on the arteries and arterioles. Similarly, with the feet initially at different temperatures vasodilatation is delayed in the cooler. The delaying action of cold may be further restricted to one digit as the

following observation shows. A comfortably cool subject immerses one hand in water at 35°C for 10 minutes thoroughly to warm all the fingers. The hand is removed, dried and a capsule through which water at 20°C circulates (5) is fitted to the proximal phalanx of the index finger, the hand is exposed and temperatures recorded from the backs of the distal phalanges of the fingers. After 5 to 10 minutes the body is warmed. In 6 observation on 3 subjects ($R T = 18-19^{\circ}\text{C}$) the rise of skin temperature began, on an average 4 minutes later in the cooled finger than in the other fingers. Since it is unlikely that the sympathetic impulses are so finely adjusted territorially as to affect adjacent fingers unequally, the delayed response must clearly be ascribed to the local action of cold on the vessels of the cooled finger. We may say then that when the body is cool and the digits are cold the arteries and arterioles of the fingers are constricted, in part by sympathetic action, in part by the direct reaction of the vessels to local temperature. If the body is then warmed, sympathetic tone lessens, the vessels widen a little and permit a stream of blood which, though faster, is at first insufficient to raise the temperature of the tissues. Eventually, as the vessels relax, the temperature of the tissues rises a little, and this rise of temperature, acting locally, further dilates the vessels and temperature now rises rapidly. The bloodflow must reach a certain minimum rate before the main response begins. Constriction of the vessels from a local cause, such as the direct action of cold will, in these circumstances, delay the beginning of the main response to loss of vasomotor tone.

Now Table I shows that the delayed rise in the toes cannot be ascribed to a difference in the initial temperatures of fingers and toes, as these were not dissimilar. We could, however, explain the delay if it could be shown either that the vessels of the feet react more strongly to local cold, or that the diminution of vasomotor tone in response to warming the body is less in the feet than in the hands. No information relevant to the first alternative is available, but evidence in favour of the second will now be considered.

In the first place we have encountered no subjects, normal or diseased, in whom warming the body failed to produce a vasodilator response in the fingers unless the sympathetic nerves were divided or the vessels structurally diseased. In many cases of severe Raynaud's disease blocking the sympathetic impulses by anæsthetisation of the ulnar nerve fails to raise the skin temperature of the 5th finger (5), in similar circumstances warming the body produces a full vasodilatation in the fingers (7). Warming the body thus seems to be more potent in producing vasodilatation in the upper extremity than can be accounted for by a simple removal of vasoconstrictor tone, for this reason it has been suggested that the sympathetic nerves to the upper limb contain vasodilator as well as vasoconstrictor fibres, the former being brought into play by a rise of body temperature (7).

Secondly, in the lower limbs warming the body seems less effective than nerve anæsthetisation in producing vasodilatation. In one of our patients, suffering from an indolent ulcer of the foot of uncertain etiology,

warming the body failed to produce a rise of skin temperature of the toes in repeated trials, spinal anesthesia, on the other hand, produced prompt and full vasodilatation. Gibbon and Landis (2) state that in two cases of

TABLE II

Subject G. P. May the 1st 1933. Subject clad in short trousers and woollen vest had been sitting in observation room with hands and feet exposed for 20 minutes before beginning the observation. He then sat in the front of the warm chamber, the arms exposed from the elbows, the feet from the ankles. Junctions were fixed to the nail bases of the digits and to the other areas enumerated. The room temperature was measured by a junction placed between the feet

Time, min.	L1 toe	Dorsum L foot	L heel	Base of L1 toe	L5 toe	R1 toe	L2 finger	R T	REMARKS
0	16.1	22.3	20.2	—	—	16.8	17.8	15.8	
10	16.2	21.9	19.3	—	—	16.5	16.7	15.7	Mouth temp 36.95°
10	Chamber complete test			Lights on					
26	16.0	21.0	19.0	—	—	16.4	16.0	15.8	Mouth temp 37.1
30	16.0	20.8	18.9	—	—	16.4	16.3	15.9	
36	16.0	20.5	18.8	—	—	16.4	16.0	16.0	Mouth temp 37.15
40	16.1	20.5	18.7	—	—	16.3	20.8	16.2	
48	16.3	20.2	18.6	—	—	16.4	21.0	16.4	Mouth temp 37.2
56	16.8	20.0	18.5	—	—	16.8	21.7	16.4	Mouth temp 37.3
64	17.2	19.8	18.4	—	—	17.1	21.7	16.5	Mouth temp 37.4
									Sweating
78	19.2	19.4	18.4	—	—	18.5	21.6	16.6	Mouth temp 37.5
									Window opened
82	19.9	19.4	18.4	—	—	18.5	21.2	16.8	
88	19.2	19.4	18.4	—	—	18.3	21.0	16.8	Mouth temp 37.55
									Sweating profuse
92	18.7	19.4	18.2	—	—	17.9	21.0	16.8	
98	18.3	19.3	18.3	—	—	17.5	20.9	16.8	Mouth temp 37.6
100	The subject came out of the warm chamber. After the sweat had been dried off he lay down on a couch with the legs exposed from the knees. The room conditions were unchanged.								
110	17.7	19.4	19.2	—	—	17.5	25.2	16.8	
120	16.8	19.2	17.9	—	—	17.0	20.8	17.0	
120	2 cc 2% novocaine injected around the 6th posterior tibial nerve at the malleolus								
132	17.0	19.2	17.8	—	—	16.9	20.1	16.9	
138	16.8	19.2	17.8	18.2	—	16.8	—	17.0	
142	17.0	19.0	17.8	18.5	—	16.8	—	17.0	Reddening and beginning anesthesia of lateral aspect of sole and 4th and 5th toes
150	17.2	19.7	17.7	19.0	27.6	16.6	—	17.0	4th and 5th toes and outer side of foot hot to touch
156	18.0	27.0	17.8	24.0	31.3	—	—	17.0	
160	19.0	27.5	17.8	27.8	33.2	—	—	17.0	Complete anesthesia L5. Partial anesthesia L1 (solar asp.)
164	21.3	25.0	18.0	32.0	31.6	—	—	17.0	
168	25.0	25.2	18.2	33.1	—	—	—	17.0	Whole sole of left foot is red except arched area which is pale. Complete anesthesia solar aspect left great toe
174	30.2	28.0	18.7	34.0	—	16.7	—	16.9	
178	31.5	28.0	21.5	34.2	—	16.8	—	17.0	
188	32.0	28.2	28.0	34.5	—	16.8	—	17.0	Mouth temp 36.95
200	31.8	28.5	30.0	34.3	—	17.0	—	17.1	
206	32.0	—	30.6	34.2	—	16.8	10.8	17.2	

acrocyanosis, warming the body failed to produce a rise of skin temperature in the feet, though the response when it occurred was normal. We ourselves have repeatedly failed to produce a vasodilator response in the feet by raising the body temperature in one normal subject (P) when the feet have been thoroughly cold. Table II compares in this subject the effects of warming the body and of anaesthetising the posterior tibial nerve. In a cool room, warming the body for 90 minutes raised the mouth temperature by 0.65°C yet failed to produce in the toes more than a transient and small rise of temperature culminating at the 82nd minute*. At the 120th minute, injection of novocaine into the region of the posterior tibial nerve at the ankle joint produced a full rise of skin temperature of the toes.

These observations strongly suggest that warming the body removes only a part of vasoconstrictor tone from the feet, the remainder being more or less permanent unless the sympathetic fibres are blocked. This partial removal of tone explains adequately the delay or failure of vasodilatation in the feet as compared with the hands. For, when the extremities are cool and the body is warmed, the incomplete removal of sympathetic tone from the vessels of the feet is less effective in overcoming the local constrictor action of cold than is the complete removal in the case of the hands.

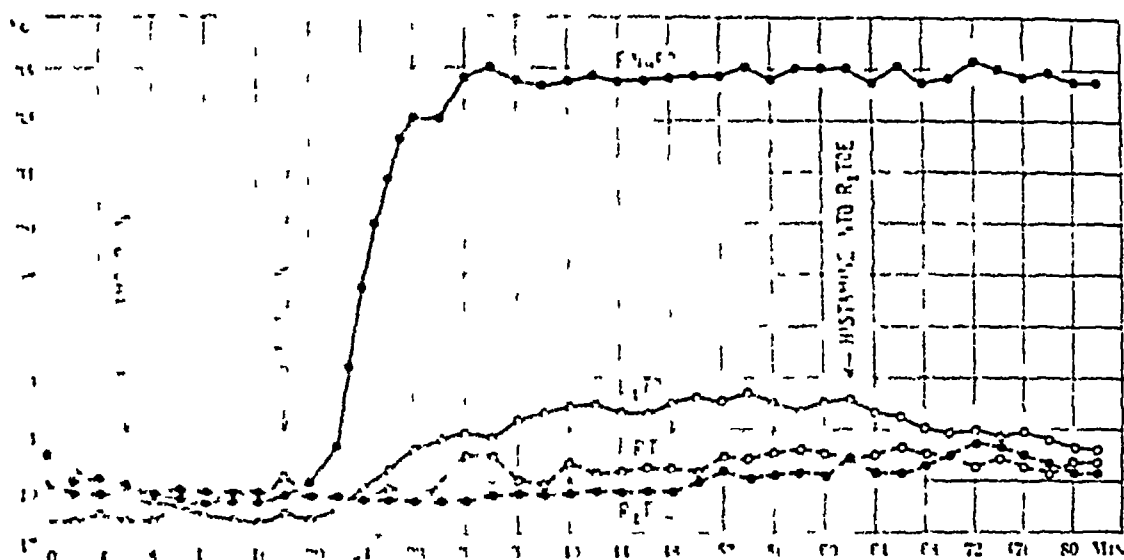
To determine the order of vessels concerned in delaying or preventing vasodilatation in the feet, we have investigated the local effect of histamine.

The effect of histamine Histamine punctured into the human skin produces a dilatation of the minute vessels and terminal arterioles (6), in the rabbit's ear it also dilates the arteriovenous anastomoses (3), and Grant and Bland have brought evidence to show that the rise of skin temperature produced by pricking histamine into the finger-tip is largely due to the opening of these vessels (4).

Histamine usually fails to raise skin temperature when pricked into the tip of the naturally cool toe. If, when the feet and hands are naturally cool, the body is warmed and histamine pricked into the tip of one great toe as soon as the response of the fingers has started, then the rise of skin temperature begins in this toe 6 to 16 minutes earlier than in the remainder (3 subjects). This result was anticipated and is to be attributed to the summation of the vasodilator action of histamine with the vasomotor response to warming the body. In one of these three subjects, P, tested on another occasion, warming the body failed to produce vasodilatation in the feet, the effect of histamine under these circumstances is shown in Fig 5. Histamine pricked into the left great toe when the response of the fingers had started, produced a rise of skin temperature of 4.7°C , beginning in 3 minutes, maximal after 36 minutes, and then subsiding. The temperature of the other great toe

* This observation incidentally shows the small margin between response and no response from the toes. For it is likely that the rise of skin temperature of the toes would eventually have gone to completion, had not a small draught been created by opening the window at the 76th minute. The resultant increased heat loss from the toes was more than enough to counteract vasomotor relaxation and the toe temperature fell again towards that of the room.

followed room temperature until, at the 62nd minute, histamine was pricked into its tip, producing a rise of 1.2°C beginning in 1 minutes, maximal in 10 minutes and then subsiding



It seems clear that in this observation, vasodilatation of the feet did not result from warming the body chiefly because the terminal vessels, probably arterioles, failed to open, when these vessels were dilated by histamine a response occurred. The smallness of the response to histamine suggests that the proximal vessels, though open, were not dilated. The failure of the terminal vessels to open, and of the proximal vessels to open widely when the body was warmed, is attributed to the loss of vasomotor tone being insufficient to counteract the local constrictor action of cold.

Comment The difference in response of the fingers and toes to warming the body is of importance clinically. It is clear that in testing the patency of the vessels of the lower extremities, an absent or incomplete vasodilator response to warming the body cannot be accepted as indicating structural disease of the vessels, an absent or incomplete response to nerve anaesthetisation is of greater significance.

Finally, we suggest that the unequal distribution of vasomotor tone to the upper and lower extremities is to be related to the assumption of the upright posture in man. Dr Grant tells us that in the rabbit warming the

body causes a simultaneous rise in the temperature of the initially cool hind and fore feet, though the rise in the hind feet is less rapid

CONCLUSIONS

1 When the extremities of normal subjects are naturally cool vasodilatation in response to warming the body becomes evident in the fingers earlier than in the toes, exceptionally, vasodilatation may fail in the feet. This difference in time relations of the responses of upper and lower extremities is less evident when these are warm.

2 The delayed response of the toe, as compared with the finger, is attributed not to a difference in time, but to a difference in intensity of the vasomotor relaxation in upper and lower extremities. Warming the body produces in the upper extremities complete, in the lower extremities incomplete, loss of vasoconstrictor tone.

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THE ALLEGED RELATION OF HYPERFUNCTION OF THE POSTERIOR LOBE OF THE HYPOPHYSIS TO ECLAMPSIA AND THE NEPHROPATHY* OF PREGNANCY

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A RAISED blood pressure and cedema are two symptoms which are commonly associated with eclampsia, and it is natural that attempts should have been made to explain the etiology of the disease in terms of two of its most striking accompaniments. Hoffbauer, in 1918, expressed the view that eclamptic convulsions were due to anæmia of the brain resulting from an arterial spasm caused by the vasoconstrictor action of the hypophysisadrenal system. Rossenbeck, in 1927, and Kustner, in 1928, brought clinical observation to the support of this hypothesis, but it was not until 1930 that Anselmino and Hoffmann furnished experimental evidence, which they considered conclusive, in favour of the hypophysis being causally involved in the disease. Two years later these writers, together with W P Kennedy, published a paper embodying a considerable amount of experimental evidence in support of the hypothesis that both eclampsia and the nephropathy of pregnancy were caused by hyperfunction of the posterior lobe of the hypophysis. It is largely with this paper that the present communication is concerned.

The authors took blood from patients suffering either from eclampsia or the nephropathy of pregnancy and treated it in the following manner: "About 40 c c of venous blood is collected coagulation being prevented by the addition of 20 c c 5% sodium citrate, centrifuged, and 1 c c normal acetic acid added to 20 c c plasma. This brings the plasma reaction to pH 3.9—4.3 as measured by the hydrogen electrode. It is then filtered under negative pressure through a filter of acetic collodion till about two thirds of the amount pass through. The ultrafiltrate having been proved to be protein-free, is kept on ice till it is used, which should be as soon as

* By nephropathy is to be understood a diffuse non inflammatory affection of the kidneys associated with the passage of albumin, and often of casts, in the urine. Most authorities are agreed that the nephropathy of pregnancy may develop into eclampsia and for this reason is often referred to as pre-eclampsia.

albuminuria and oedema, will neither develop eclampsia nor die even if they remain untreated. The contention of Volhard that in these cases a rise in the systolic blood pressure invariably precedes albuminuria has been proved to be untrue (Irving, Theobald, 1929). It is, moreover, well known that women usually suffer from constipation during the latter months of pregnancy, and this is particularly true of these patients. If the nephropathy of pregnancy were due to posterior pituitary hyperfunction it might have been expected that the bowels would have been over-active, seeing that even 0.5 unit of "infundin" (Messrs Burroughs, Wellcome and Co.) injected subcutaneously into a healthy man usually causes an evacuation. Again, it is generally accepted that in these patients the daily output of chloride in the urine is usually considerably less than the daily intake, whereas during the subsequent postpartum diuresis the converse is true (de Wesselow and Wyatt, 1924). If the unknown substance in the ultrafiltrate when injected into rabbits caused an increase in the percentage of chloride in the urine, it might have been expected that it would have the same effect in the patients from whom the blood was withdrawn. It is unfortunate that the authors did not publish the quantities of urine secreted by their patients, nor the daily amounts of chloride received and excreted both before and after delivery.

In spite of the improbability, as derived from preceding considerations of a causal connection between posterior pituitary function and the nervous and vascular phenomena associated with eclampsia, it seemed advisable, in view of the favourable reception it has received, that the work of Anselmino, Hoffmann and Kennedy should be subjected to critical survey. In this connection three points of interest and importance emerge. First, if the authors' results are significant one must assume that in the post-pituitary extract used by them the relationship between the anti-diuretic activity on the one hand, and the oxytocic activity on the other, shows a general correspondence with that encountered in other post-pituitary extracts. This assumption is indeed implicit in the estimates made by them. Second, their hypothesis depends upon the pressor and anti-diuretic activities being distinct entities. Bijlsma, Burn and Gaddum (1928) estimated the amounts of oxytocic, pressor and anti-diuretic substances present in four different commercial pituitary extracts and compared them with those present in a standard powder. The amounts of anti-diuretic substance in the preparations did not run parallel with either the oxytocic or the pressor functions and the conclusion drawn was that the anti-diuretic effect of posterior pituitary extract was due neither to the pressor nor to the oxytocic principle. The following sources of error may, however, be noted in the methods used by these and other authors (Mohtor and Pick (1926), Anselmino and Hoffmann) for assaying the anti-diuretic potency of post-pituitary extracts: (1) The pituitary extract is injected subcutaneously, thereby introducing unknown, incalculable and avoidable factors, (2) the extract is injected at the same time as the water is given there is

therefore no guarantee that normal diuresis would have occurred if the extract had not been injected, (4) no emphasis is laid on the necessity for hydrating the tissues previous to the test, without which precaution, in our experience, no accurate assay can be made. It may therefore be concluded that the methods so far used for the assay of the anti-diuretic substance are not sufficiently accurate to determine whether or not the pressor and anti diuretic activities are derived from a common principle.

The last of the three points to which reference has been made is that Anselmino, Hoffmann and Kennedy made no control observations with the object of showing that the results they obtained with their ultrafiltrates could, with reason, be attributed to the presence of pituitary activity in the blood. It is with this point that the experiments described in this paper are chiefly concerned. They were undertaken with a view to determining (a) the minimum amount of posterior pituitary extract which would inhibit water-diuresis in man and in the dog, (b) the amount of the extract which would raise the blood pressure in man, (c) the permeability of different collodion membranes to the anti-diuretic oxytocic and pressor activities of the extract, (d) whether any anti-diuretic activity is present in the ultrafiltrate of blood withdrawn from eclamptic patients. These investigations will now be described.

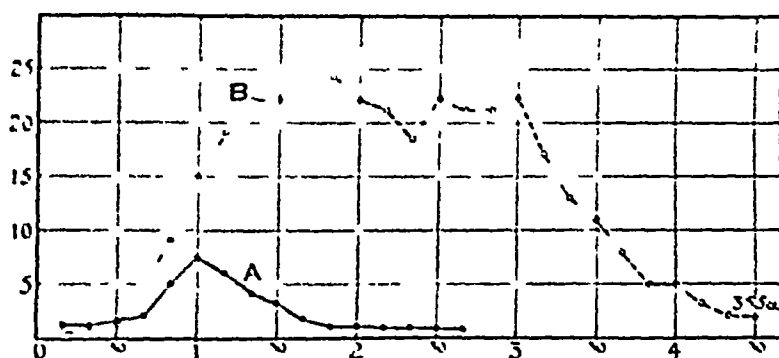


Fig. 1. Curves to show necessity for administering a standardised hydrating dose of water. Curve A shows response to 250 c.c. water. At the end of this period a further dose of 250 c.c. of water was given, the output being represented by Curve B. Water was in the trough in the cage before the experiment was commenced so that the animal was presumably not thirsty. Conversely, animals have been observed to drink water when returned to their cages half an hour after receiving 250 c.c. of water through the stomach tube. It is evident that a measure of dehydration of the tissues occurs apart from producing a sensation of thirst. On each occasion the water was given at zero time. Ordinate, each point represents the amount of urine secreted in the preceding 10 minutes and expressed in c.c. Abscissa, time in minutes and hours.

A. *The minimum amount of posterior pituitary extract which inhibits water-diuresis in man and in dogs.* The results obtained in dogs will be recorded first. Bitches on which a plastic operation exposing the urethral orifice (Klischek, Pickford, Rothschild and Verney, 1933) had been performed were used. Two hours after an animal had been given a standard dose of

250 c c of tepid water through a stomach tube, it was placed in a Parlov stand. A soft rubber catheter was introduced into the bladder and the urine collected in a graduated glass cylinder, the amounts being recorded at ten minute intervals. When the urine-flow had returned to its resting rate, a further 250 c c of water were administered in a similar manner (see Fig 1). About one hour later, near the peak of diuresis, the posterior pituitary extract was injected intravenously*. The preparation used was "infundin" (Messrs Burroughs, Wellcome & Co), its oxytocic content being standardized in international units, in fractions of which the doses injected are expressed. Several boxes of the same batch of extract were obtained and kept in cold store until they were required. Five units of "infundin" were diluted in physiological saline solution to make 10 c c. From this dilution 1 c c was taken and added to 9 c c of saline solution, and in like manner successive dilutions were made, the standard amount injected being 1 c c.

Three types of interruption in the diuresis curve may follow the injection of the extract. (1) *Maximal inhibition*, the urinary secretion falling to less than the normal resting rate and remaining at this level for a prolonged though variable period of time, in all such cases the urine is found to contain albumin and frequently blood during part or the whole of the period of inhibition (Fig 2, curves A and B). (2) *Minimal inhibition*, the rate of urinary secretion falling to approximately the resting rate for a few minutes, and then gradually increasing until an hour later it again reaches a maximum which may be little less than that which obtained at the peak of diuresis (Fig 2, curves C and D). (3) *Partial inhibition*, the rate of urinary secretion either falling slightly for a few minutes and then returning to the normal, or falling to perhaps half the usual rate and remaining at about that level until diuresis is complete.

It was found that if the tissues of the animal were hydrated in the manner described, and the extracts were injected intravenously at approximately the same rate and at about the same interval of time after the second dose of water had been given,† the amount of "infundin" necessary to cause minimal inhibition of diuresis was remarkably constant for each animal, but varied in different animals from 0.0005 to 0.01 unit (Figs 2 and 3, cf Winton, 1931, page 160). The amount of "infundin" necessary did not, however, bear any obvious relation to the size of the animal, for one of the smallest dogs required the largest dose, while the largest dog was sensitive to the smallest amount.

* Intravenous injections were made into the dorsal metatarsal vein through a very fine (No. 20 or smaller) hypodermic needle. The dog stood quietly in the stand during the injections and on no occasion was any emotional disturbance produced by them. Moreover the absence of any effect on the rate of urine flow of injections of physiological saline has been demonstrated repeatedly.

† Smaller amounts of 'infundin' sufficed to cause minimal inhibition if the injection was made some time after the peak of diuresis was passed. Conversely larger amounts were necessary if more than the standard dose of water was given.

varied from 0.005 to 0.01 unit, although in one man 0.0005 unit sufficed. In the practical classes of this department 0.5 unit of "infundin" is injected subcutaneously after a student has swallowed a litre of warm water, and experience with considerable numbers of men and women students shows that diuresis is thereby invariably inhibited for at least three hours. It was also found that 0.05 unit of "infundin" injected intramuscularly caused maximal inhibition of diuresis, although no attempts were made to measure the period of time for which it remained effective. It was thought possible that a woman towards the latter end of pregnancy might be more tolerant to posterior pituitary extract, but even here it was found that between 0.005 and 0.01 unit of either "infundin" or "pituitrin" (Parke, Davis & Co.) sufficed to cause minimal inhibition of water diuresis, a range of dose corresponding closely with that found in normal man and in dogs (Fig. 4).

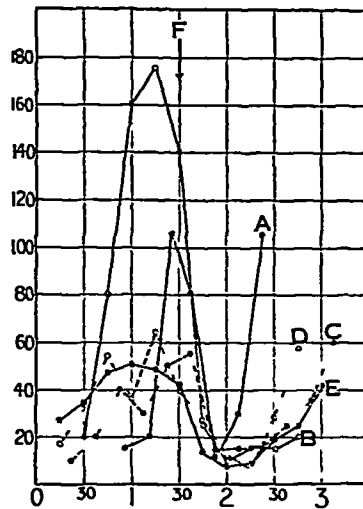


Fig 4 Diuretic responses of pregnant women, within two weeks of term, to 750 cc of water by mouth. 0.005 unit "infundin" was injected intravenously at F, curve D, 0.005 unit "pituitrin" at F, curve E, 0.01 unit "infundin" at F curves B and C. Note the conspicuous differences in the degree of response to water in apparently healthy pregnant women. A = diuretic response of male student to 1,000 cc water by mouth. 0.01 unit "infundin" being injected intravenously at F. On each occasion the water was given at the time the curve begins. Abscissa as in Fig 1 g r. Ordinate as in Fig 1 except that the urine was measured at 15 instead of 10 minute intervals.

B *The amount of post-pituitary extract necessary to raise the arterial blood pressure in man and in dogs* Oliver and Schäfer, reported in 1895, that extracts from the pituitary body when injected intravenously into anæsthetized animals caused an elevation of the blood pressure and a slight slowing of the heart rate. Even large doses of this extract, however, failed to cause the same rise in the blood pressure as a small dose of adrenalin, although the effects produced lasted for a longer time. All subsequent

work has confirmed these original observations and it is generally agreed that post pituitary extract when injected subcutaneously or intramuscularly has no effect on the blood pressure. There is, however, a considerable divergence of opinion concerning the effects caused by the injection of post-pituitary extract into normal man and the unanesthetized dog. A careful perusal of the work of several authors (Cland and Porak (1913), Behrenroth (1914), Lechke (1919), Roscnow (1919), Sacks (1921), Gruber (1929), Ross and Stehle (1930), Melville (1931)) allows but one unequivocal fact to emerge. It is the impossibility of causing a marked elevation of the arterial blood pressure above the normal in man or in dogs by the intravenous injection of post pituitary extract, for if large amounts of the extract are injected the blood pressure falls and death may ensue. The extract constricts the coronary vessels and according to Lechke (1919) causes sino auricular block. Moderate elevations of both systolic and diastolic blood pressures may be caused by relatively small doses of the extract, but only if it be injected intravenously. Sacks (1921), however, using the cuff method on a number of volunteers, reported that the subcutaneous injection of from 0.5 to 1.0 c.c. of "infundin" caused a transient rise of blood pressure, which commenced at the end of the first minute and reached its maximum in three minutes. The average rise in the systolic pressure was 9 mm. and in the diastolic 12 mm.; it may be added, in parenthesis, that Sacks found that "infundin" conspicuously decreased the rate of oedema formation. I have injected 5 units of "infundin" into one student, 10 units into two others and 10 units of "pituitrin" into a female patient, all the injections being intramuscular, and on no occasion was any significant change in either the systolic or the diastolic blood pressure detected. I have further been unable to detect any change in the arterial blood pressure after the intravenous injection into man of amounts of "infundin" which were sufficient to cause minimal inhibition of water-diuresis. For the purpose of this paper it suffices to assert that there is no experimental evidence to justify the assumption that the posterior pituitary pressor substance could elevate the systolic blood pressure from the normal to over 180 mm. Hg and maintain it at that level indefinitely, while all the available evidence goes to show that no marked elevation of the blood pressure can be caused by post-pituitary extract, for if large amounts of the extract are used the blood pressure falls incontinently. Now, Anselmino, Hoffmann and Kennedy found that the ultrafiltrates from the blood of patients whose systolic blood pressure exceeded 180 mm. Hg when injected subcutaneously into anesthetized rabbits invariably caused a rise of blood pressure. In the protocol published 12 c.c. of the ultrafiltrate caused a rise of 26 mm. Hg in the blood pressure, which was not attained until 35 minutes after the injection had been made. They state that the subcutaneous injection of posterior pituitary extract has no effect on the blood pressure of an anesthetized rabbit, but suggest that the pituitary pressor substance circulating in the blood is so much more potent than the extract made

from the gland that "this difference is not an important one" Seeing that all that is known about posterior pituitary pressor activity is known as the result of experiments made with extracts made from the gland, the authors can hardly expect this suggestion to meet with acceptance. Whatever may be the cause of the rise in blood pressure found experimentally by them it is clear that they were not justified in ascribing it to post-pituitary pressor activity.

C *The permeability of different collodion membranes to posterior pituitary extract* The first set of experiments was made with alcohol-ether collodion bags. The preparation used was Celloidin (Schering) of which 15 g were dissolved in 225 c c of absolute alcohol and 75 c c of ether. The bags were made at room temperature on a revolving, slightly tapering glass tube, the layers being applied at 10 minute intervals. After the requisite number of layers had been applied, varying from 4 to 8, the tube was kept rotating for one hour before being immersed in tap water. It was left in this overnight, after which time the removal of the bag from the glass tube was a simple matter. The number of layers applied determined the strength but did not significantly alter the permeability of the bag. One c c (10 units) of "infundin" added to 9 c c of physiological saline solution was introduced into the bag, and filtered under negative pressure supplied by a water pump. On no occasion did the ultrafiltrate, even up to a volume of 3 c c, contain an amount of anti-diuretic activity which could be detected by the method on dogs described above. In order to make the bags more permeable, the interval between applying the layers was reduced to 8 minutes, and the final time of drying from 1 hour to half an hour. The bags so made remained equally impermeable to the anti-diuretic substance. On a few occasions the oxytocic and pressor activities of these ultrafiltrates were tested and found to be absent. In a private communication one of the authors (W P K) stated that the filters he used were made by running a 10 per cent solution of collodion in glacial acetic acid into a sintered glass Buchner filter. Five units of "infundin" were therefore added to 9.5 c c of physiological saline solution and passed through such a membrane. Each cubic centimetre of the ultrafiltrate contained less than the anti-diuretic activity associated in the original extract with 0.01 oxytocic unit. On one occasion 5 units of "infundin" were added to 9 c c of blood plasma, which was acidified with 0.5 c c of normal acetic acid, and passed through an acetic collodion filter. The ultrafiltrate on this and on other occasions contained no appreciable amount of anti-diuretic substance (Fig 5, curves A and B). Finally, an "Ultra-cellaflita" membrane, grade "Fein," 9 cm in diameter, was used in a Zsigmondy filter-apparatus, and it was found that the protein-free ultrafiltrate of "infundin" in physiological saline solution obtained under negative pressure contained considerable amounts of the pressor and anti-diuretic activities. Its oxytocic content was not investigated. This membrane is advertised to hold up benzopurpurin, which has a molecular

weight of about 800. The permeability of this membrane to pituitary extract having been demonstrated 10 units of "infundin" were added to 50 c.c. of blood (citrate 1) withdrawn from pregnant women. The blood was centrifuged and 1 c.c. of normal acetic acid was added to 20 c.c. of the plasma, which was then passed through the filter. Assuming the "infundin" to remain in the plasma and all of the activity to pass through the filter, each cubic centimetre of the ultrafiltrate should have contained the anti-diuretic activity associated in the original extract with 0.4 oxytocic unit. It will be seen from Fig. 5 curve D that 1 c.c. of the ultrafiltrate

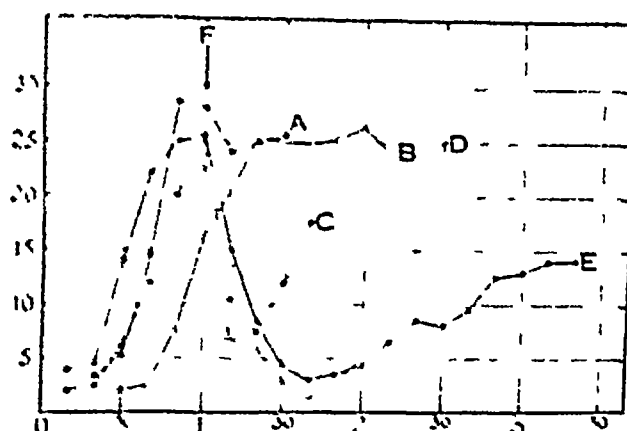


Fig. 5. A shows the absence of effect on water-diuresis of the injection of 1 c.c. of ultrafiltrate (acetic collodion filter) from plasma containing 0.2 unit of "infundin" per c.c., B, that of the injection of 1 c.c. ultrafiltrate (acetic collodion filter) from the plasma of human blood taken during pregnancy and containing 0.2 unit of "infundin" per c.c. of blood, C shows the inhibition produced by the injection of 1 c.c. ultrafiltrate (Cellafilta) from plasma to 10 c.c. of which 5 units of "infundin" had been added, and D that produced by the injection of 1 c.c. ultrafiltrate (Cellafilta) from the plasma of blood to 50 c.c. of which 10 units of "infundin" had been added. E shows the inhibitory effect of 0.02 units "infundin". All injections were made intravenously at 1'. Each curve is the response in the dog to 250 c.c. water given by stomach tube at the time the curve begins. Ordinate and abscissa as in Fig. 1, q.

contained less than the anti-diuretic activity associated with 0.02 unit. Similar results were obtained on several occasions. By washing the red blood corpuscles with physiological saline solution, centrifuging, and passing the supernatant fluid through the filter, it was proved that a considerable proportion of the anti-diuretic activity had been adsorbed by the corpuscles. Similarly it was possible to show that some of the activity had been adsorbed by the proteins of the blood plasma.

D. *The ultrafiltrate of blood withdrawn from eclamptic patients.* At the conclusion of these experiments it was decided to determine whether any anti-diuretic activity could be demonstrated in the ultrafiltrate of blood withdrawn from a patient suffering from eclampsia. The plasma obtained from two such patients was filtered through alcohol-ether collodion bags, and on each occasion 3 c.c. of the ultrafiltrate were found to contain

an anti-diuretic activity roughly commensurate with that present in 0.005 unit of "infundin" (Fig 6). One litre of the patient's plasma would therefore have contained as much anti-diuretic activity as is present in from 1.5 to 2 units of "infundin". The anti-diuretic substance present in the ultrafiltrate was unstable, for although it was kept in the ice-chest at a temperature below 0°C , most of its activity had disappeared when tested a fortnight later*. There can be little doubt that this was the substance found by Anselmino, Hoffmann and Kennedy, and seeing that it passed through a filter known to be impermeable to all three activities of "infundin," it could not have derived from the posterior lobe of the hypophysis. It is possible that it may prove to be identical with the anti-diuretic substance extracted from the liver by Theobald and White (1933).

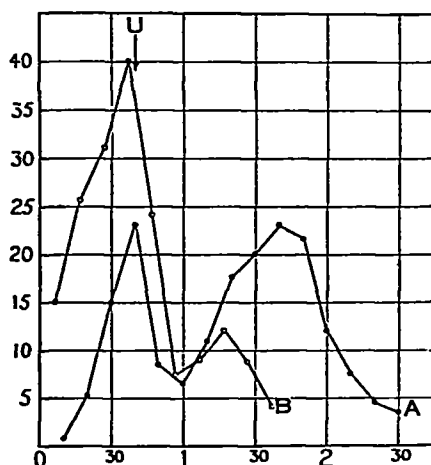


Fig 6 To show inhibition of water-diuresis by the intravenous injection of 3 c.c. ultrafiltrate from the blood of two eclamptic patients. The filter used was impermeable to the anti-diuretic activity of post pituitary extract. Injections were made at U. Ordinate and abscissa as in Fig 1, q.v.

Discussion

Hyperfunction of the posterior lobe of the hypophysis could not account for the syndrome of eclampsia, but only for a diminished secretion of urine and a small elevation of the blood pressure, signs which are frequently but by no means invariably associated with the disease, while leaving unexplained the fact that the patient suffering either from the nephropathy of pregnancy or eclampsia almost invariably suffers from a true retention of chloride and constipation. It has been shown that in pregnant women near term the intravenous injection of from 0.005 to 0.01 of a unit of either "infundin" or "pituitrin" inhibits water-diuresis at its peak (Fig 4), when the con-

* The anti-diuretic activity has not disappeared so rapidly from other eclamptic blood ultrafiltrates which have been tested more recently. I should here like to take the opportunity of expressing my gratitude to Dr W. H. Oxley for sending me material from toxæmic patients under his care at the East End Maternity Hospital.

centration of anti-diuretic substance in the blood is presumably minimal. Most women suffering from the nephropathy of pregnancy respond, although to a diminished degree, to the ingestion of water, while the response in normal women near term is usually very much lower than in the non-pregnant state. If the post-pituitary water diuresis hypothesis developed by Khsucki, Pickford, Rothschild and Verney (1933) be accepted, it follows that in man, the pregnant woman not excepted, the normal variation in the amount of anti-diuretic substance in the blood would be represented by not more than 1 part of 'infundin' (10 units per c.c.) in 5×10^6 parts of blood, and that this amount of substance must disappear from the blood before water diuresis can occur normally. Further, if the diminished renal response to the ingestion of water associated with the nephropathy of pregnancy be causally associated with the posterior pituitary gland, it could be explained by postulating either the partial failure of the mechanism which causes the disappearance of anti-diuretic substance from the blood, or by an increase of this substance in the blood over the concentration normally present at the height of water-diuresis, by an amount not greater than that present in 0.01 unit of 'infundin'. Anselmino and Hoffmann were unable to detect any anti-diuretic activity in blood withdrawn from healthy pregnant women, and the following calculation makes it evident that the excess of this principle over that normally present at the height of water diuresis, and sufficient to cause its immediate inhibition, could not be detected by the method used by them. Assuming the nephropathic patient to possess 5 litres of blood it follows that not more than the anti-diuretic activity associated with $10/5000 \times 0.01$, or 0.00008 of a unit in excess of the normal threshold can be present in the 40 c.c. of venous blood withdrawn, and less than half that amount in the 10 c.c. of ultrafiltrate injected by the authors assuming that there was no loss. Seeing, however, that even when the concentration of 'infundin' in the plasma is very high, no appreciable amount of the anti-diuretic substance passes through the acetic collodion filter, it is evident that the amount of anti-diuretic substance in the ultrafiltrate when the original plasma only contained an excess of 0.00008 of a unit would be infinitesimal. Taking into account the high potency of the post-pituitary anti-diuretic substance the assertion of Anselmino and Hoffmann that from 3 to 10 units of pituitary activity may be present in a litre of blood plasma (from 7.5 to 25 units in the total blood) becomes incredible.

Reasons have been advanced for the belief that the methods of assay of the anti-diuretic principle are not sufficiently accurate to justify the conclusion of Bylsma, Burn and Gaddum that the anti-diuretic effect of posterior pituitary extract is due neither to the pressor nor to the oxytocic principle. These authors found that the oxytocic and pressor substances were present in four commercial extracts in remarkably constant proportions. Although the oxytocic and pressor fractions may be separated, the anti-diuretic following the pressor principle, I have found the amounts of anti-diuretic

substance in three different post-pituitary extracts to be very constant notwithstanding the fact that "infundin" is only standardized in oxytocic units. This conclusion agrees with that reached by Burn (1928). Since it requires a much larger amount of post-pituitary extract to cause a significant, albeit transient elevation of the blood pressure than to inhibit water-diuresis it is somewhat astonishing that the posterior pituitary gland does not contain a much higher amount of the pressor substance. Indeed, unless it can be shown that a larger proportion of the pressor than of the other substances is lost during extraction, it raises the issue as to whether the pressor substance is in fact normally concerned with *pressor* activity in the body. The facts that it constricts the coronary vessels and depresses the heart muscle, that the intramuscular injection of 10 units into man has no effect on either the systolic or the diastolic blood pressure, and that its intravenous injection into unanesthetized dogs causes a fall in blood pressure unless relatively small doses are given (2 units) tend to support this doubt. Indeed, it might be advanced with reason that there is no reliable evidence in favour of the view that the pressor and anti-diuretic substances are distinct, and there is no evidence that the different activities are ever secreted in widely varying proportions. It has already been pointed out that the hypothesis under consideration of necessity postulates these two assumptions, and must, apart from all other considerations, fall to the ground if they are false. The hypothesis, however, is finally disproved by the fact that the anti-diuretic substance present in the ultrafiltrate of blood withdrawn from eclamptic patients passes through a membrane known to be impermeable to posterior pituitary extract. Seeing that this substance is not present under physiological conditions, there is no reason to assume that its anti-diuretic activity would be as potent in man as in dogs. We have, however, not yet put this question to the test of experiment.

SUMMARY

1 The syndrome of eclampsia could not be explained by postulating hyperfunction of the posterior lobe of the hypophysis. Moreover the hypothesis leaves unexplained the fact that the patient suffering either from the nephropathy of pregnancy or from eclampsia almost invariably suffers from a true retention of chloride and constipation. Further, according to Sacks (1924) "infundin" conspicuously decreases the rate of oedema formation.

2 The hypothesis postulates not only that the pressor and anti-diuretic activities of the extract are separate, but that they may be secreted in widely varying proportion. Neither of these assumptions is supported by reliable evidence.

3 A method of assaying the anti-diuretic potency of posterior pituitary extracts is described. It is shown that minimal inhibition of the diuretic

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THE RELATION OF HYPERCHOLESTERINÆMIA TO INCREASED TOLERANCE FOR THYROID PREPARATIONS IN NEPHROSIS

By R S AITKEN

(From The Medical Unit, The London Hospital)

IN 1922 Epstein (3) advocated treatment with thyroid preparations for the condition which he had described in 1917 as nephrosis. In 1926 (4) he described several examples of recovery following this treatment, and he remarked on the absence of any untoward effects after unusually large doses of thyroid. Other observers have reported similar recoveries, and have also noted the surprisingly great tolerance of their patients for thyroid: thus Murphy and Warfield (8) speak of "enormous tolerance for thyroid extract," after giving 60 to 75 grains daily; McClendon (6) gave 9 or 10 grains of thyroid extract daily in three cases of nephrosis in children and they all recovered, with a *fall* in their pulse-rates after the treatment, and Mouriquand, Schoen, Naussac and Bouchon (7), who gave up to 15 grains (1 gm) of thyroid extract daily with good effect to a nephrotic child of five, speak of a "remarkable tolerance." The most accurate measure of this tolerance, however, is to be found in Epstein's own 1926 paper (4). His second case received on an average 5 mg thyroxin intravenously every week for two months, the basal metabolic rate, measured at intervals during that time, was -22, -13, -12, -24, -20 (per cent). His third case received 10 mg thyroxin intravenously, nine times, at intervals which were shortened from 12 or 13 days down to 4 or 5, the basal metabolic rate, except for one (inconsistent) record of +20, remained between -19 and normal. The patient was then given 20 mg thyroxin intravenously, twice, at 4-day intervals, after the first injection the basal metabolic rate rose from -12 to +4, and after the second to +12. If these figures be compared with those shown below in the diagram, from Boothby and Sandford (1), who injected thyroxin intravenously in normal subjects and obtained a rise of 17 or 19 after a single injection of 8 mg, it will be clear that they support the clinical observation of an increased tolerance for thyroid preparations in nephrotic patients.

Epstein (4) did not investigate the mechanism of this phenomenon but merely mentioned the three theoretical possibilities, namely, defective absorption of the thyroid principle by the tissues, inactivation of it by some

enlarged ("hobnail") liver Gall-bladder and bile ducts were normal The kidneys showed œdema, congestion, jaundice, and parenchymatous degeneration, but none of the changes associated with nephritis or nephrosis The thyroid was normal

Determinations of this patient's basal metabolic rate were made in January 1930, using the Douglas bag method, the Haldane-Henderson gas analysis apparatus and the Aub and Dubois standards The patient slept in a single room, the gas samples were collected immediately after she awakened in the morning, with a minimum of disturbance, she was a phlegmatic person and soon became used to the procedure Measurements and analyses (in duplicate) were made by an experienced worker, and full precautions against error were taken throughout The respiratory quotient

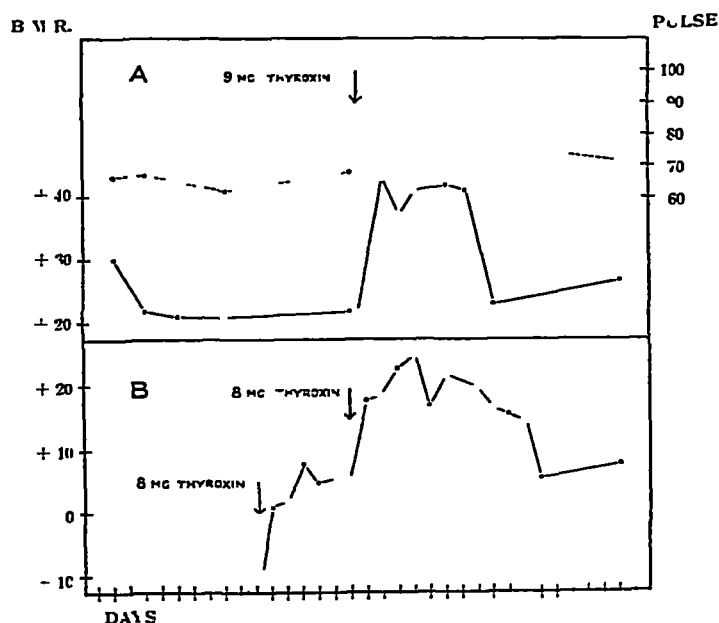


Fig 1 Effect of intravenous thyroxine on pulse (dotted line) and basal metabolic rate (continuous line) in (A) patient with hypercholesterinaemia and in (B) Boothby and Sandiford's normal man

in every determination but one lay between 0.78 and 0.81, in the one case it was 0.89, indicating overbreathing, and the observation was discarded In these circumstances the experimental error may be expected to be much less than the accepted 10 to 15% of routine basal metabolic rate determinations by less accurate methods The results are shown in Fig 1, where the close agreement of the control observations (after the first) in the fore-period shows that variations due to experimental error physiological and otherwise, are not more than 1 to 2% of the total gas exchange The patient's basal metabolic rate was high, +21 Intravenous injection

THE EFFECT OF A DIET OF PURE GLUCOSE ON THE FLUID BALANCE OF THE BODY

By F B BYROM*

(From the Medical Unit, London Hospital)

It has been realised for many years that changes in the quality of the diet cause marked alterations in body weight. In 1769 William Stark (10) in the course of a protracted series of observations on himself, found that he gained eight pounds in five days after changing from a protein (meat) diet to one composed mainly of carbohydrate (flour). The interpretation of Stark's results is rendered difficult by the fact that he suffered during his experiments from intermittent diarrhoea and scurvy (which ultimately proved fatal) and by his ignorance of the caloric equivalents of various foodstuffs. Using more modern methods Benedict and Milner (1) in 1907 found that the substitution of fat food for carbohydrate caused an immediate and substantial loss of weight, which they proved to be due to loss of body fluid. The reason for this change is still obscure, but it is now a well established fact that the absolute level of the body fluid reserves varies directly with the percentage of carbohydrate in the diet.

During the past two years a number of diabetic patients in the dietetic ward of the London Hospital have been restricted, for therapeutic reasons (4), to a diet composed of pure glucose dissolved in distilled water, for periods of from five to ten days. The daily intake of glucose varied, in different cases, between 480 and 600 g, administered in equal hourly or two hourly doses throughout the 24 hours. Insulin was given simultaneously in sufficient quantity to prevent, in most cases, glycosuria or ketosis. The subjects were for the most part confined to bed and were allowed to drink extra distilled water at will. In some instances the patient was at first restricted to a fixed balanced diet, isocaloric with the glucose diet, for a preliminary period of several days.

In view of the facts mentioned above it was somewhat surprising to find that this exclusively carbohydrate diet invariably caused an immediate loss of body weight amounting to several pounds. A sudden loss of weight of this degree, in the face of an adequate caloric intake of 2,400 calories daily, is likely to be due, substantially, not to destruction of body tissue, but to loss of body fluid. It was therefore decided to examine the fluid

* Best Memorial Research Fellow. The writer is indebted to Professor Arthur Ellis and Dr O Leyton for clinical material.

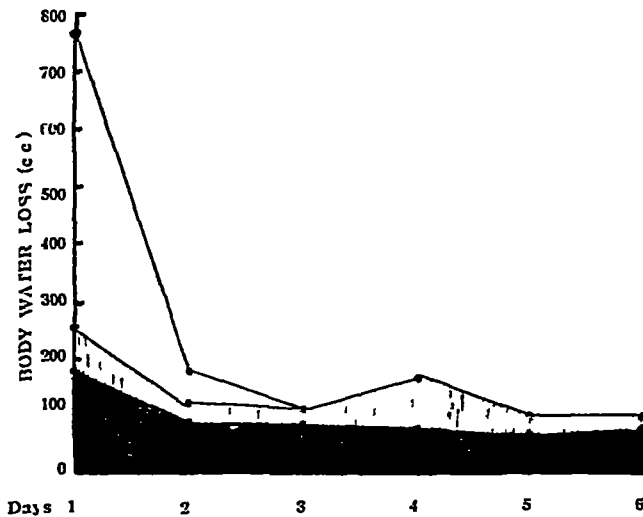


Fig 1 *Effect of a glucose diet on body fluid balance (Case 3)* Extracellular water loss is represented by the unshaded area, intracellular loss attributable to destruction of body protein by the black area, and the additional intracellular water loss (see text) by the shaded area

reserves of the cell, and it is reasonable to expect that some of the water which holds this protein in colloidal solution will be discarded as superfluous. But when the fullest possible credit is allowed to this factor, by assuming that the water of the cell is all bound physically to protein* and that an equivalent quantity of the former is excreted when the latter is mobilised, not more than one-half to two-thirds of the intracellular water loss is explained (Table I, columns (b) and (c)).

Some light is thrown on the cause of the surplus loss by the fact that Gamble, Ross and Tisdall (6) observed precisely similar changes in starvation. In the later stages of a fast the cell water loss, as measured by the potassium output, can be entirely accounted for by destruction of cell protein as measured by the nitrogen excretion. In the earlier days of the fast, however, an unexplained additional loss of cell water occurs. Gamble and his associates suggested that this initial surplus loss might be due to shrinkage of the cell following mobilisation of its glycogen reserves. The fact that a similar loss has occurred in the present experiments, where the carbohydrate intake has been high enough to exclude any reasonable possibility of encroachment on the glycogen reserves, is opposed to this explanation, and it becomes necessary to seek some other variable which is common to both circumstances.

A more attractive possibility is that potassium restriction might be the responsible common factor in question, arguing from the analogy that sodium

* The cell water loss attributable to destruction of cell protein has been calculated on the assumption that the N:H₂O ratio of protoplasm is about 4.5 per cent (Gamble, Ross and Tisdall)

TABLE I
The effect of various diets on the retention of water and electrolytes

Case No	Period (Days)	Water and Electrolytes					Common	
		Na Intake (total, g)	K Intake (total, g)	Sodium Balance (g)	Potassium Balance (g)	Water Balance (g)	Intake (g)	Excretion (g)
1	5	—	—	-7.40	-5.13	-22.9	-1300	-2.010
1	10	—	—	-9.10	-6.78	-33.5	-1400	-73.0
2	5	—	—	-3.93	-3.31	-21.0	-910	-1000
3	6	—	—	-2.57	-3.64	-26.5	-470	-1370
4	6	—	—	-3.26	-2.78	-10.0	-70	-1700
5	5	—	—	-3.27	-3.78	-11.9	-650	-1520
5	10	—	—	-1.88	-5.02	-29.6	-770	-1900
5	5	2.0	7.5	-0.60	-0.07	-21.4	-170	-200
6	3	—	1.3	-3.18	-1.44	-19.8	-530	-1130
7	3	1.5	—	+2.05	-3.30	-11.6	+820	-70
8	5	26.9	—	-25.70	-4.55	-17.4	+7000	+6700
9	6	10.8	8.1	+14.01	+3.58	-10.5	+3850	+3320

The negative signs indicate loss from the body of mm ml, nitrogen, or water, the positive signs indicate retention

restriction depletes the extracellular fluid reservoirs. This explanation was accordingly tested, in further experiments, by maintaining the potassium intake unchanged during the glucose period, the requisite amount of potassium phosphate or chloride being added to the glucose solution. In some of these cases a small quantity of potassium was excreted by the bowel in small fluid stools, these were collected and analysed for K, Na and N. It will be seen in the table (Cases 5 and 6) that when the potassium intake is maintained in this way the surplus loss of cellular water no longer occurs, in fact, the estimated cell water loss falls short of the loss attributed to destruction of cell protein. In case 9, moreover, an actual retention of 720 c.c. of cell water occurred, in the face of an expected deficit of 680 c.c. from destroyed protein.

Discussion

Theoretical Gamble's principle, on which the above estimates of fluid exchange are based, has been proved to hold good in the case of the extracellular compartment, for extracellular fluids have been obtained for direct analysis in many different forms of morbid dehydration and cedema and have been shown to contain approximately normal concentrations of base (Na).

In the case of the cellular compartment, direct proof is not possible, because cellular water cannot be obtained for analysis during life, and even after death it is not easy to exclude contamination with extracellular fluid. But it is reasonable to infer that an unvarying concentration of base in the fluid outside the cell membrane implies equal stability within the cell. If this inference is correct, that is, if potassium exchange is accepted as the most accurate measure of cellular fluid balance at present available, it follows from the results described above that loss of cell protein does not necessarily mean loss of cell water, or, in other words, that if destruction of protein involves the liberation of water from physical combination, the released water is not necessarily discharged from the cell. Peters and Laviertes (7) have recently protested against the narrow conception that the water of the cell is physically bound in mathematical proportions to the cell colloids and the present results lend direct support to their argument. The absolute level of the cellular water reservoirs is clearly at the mercy of several independent variables, of which protein storage is only one. A quantitative relationship between protein and water losses is therefore to be expected only when these other factors remain constant. The list of the other factors concerned is incomplete, but it certainly includes the acid base balance (5), probably the water intake, and possibly the glycogen balance. To this list must now be added the potassium intake. The cell evidently maintains a reserve of water in excess of its basal needs, and sudden curtailment of the potassium intake reduces the level from the optimum towards the minimum.

Practical Inferences It is generally recognised that one of the most serious complications of diabetic coma is extreme dehydration. The modern treatment of coma consists essentially of a regime of glucose and insulin. It has been shown above that such a regime not only prevents reaccumulation of the lost fluid but actually tends to cause further loss. The present observations therefore emphasise the importance of ensuring an adequate mineral intake in such circumstances. The possible methods of meeting this indication have been discussed in another communication (3).

SUMMARY

THE INFLUENCE OF DIET ON THE SUGAR TOLERANCE OF HEALTHY MEN AND ITS REFERENCE TO CERTAIN EXTRINSIC FACTORS

By H P HIMSWORTH *

(From the Medical Unit, University College Hospital, London)

THE glucose tolerance curve, is of such importance in clinical chemistry that a knowledge of the factors which may, or may not, influence it is of considerable moment. For a few years after its introduction it was thought to offer a definite criterion as to the presence or absence of diabetes, but after this time papers appeared in increasing numbers showing that the test was by no means as specific as was at first supposed. The majority of those papers dealt with the influence of endocrine diseases other than diabetes mellitus upon the test and with these intrinsic factors we shall not deal in the present paper. The minority of the publications, however, reported the influence of certain extrinsic factors on the tolerance curve of healthy individuals and the results recorded in this communication concern these factors exclusively.

From time to time claims were made that the nature of the diet had a pronounced influence on the glucose tolerance. In 1927 Sweeney (17) published results showing the effect of carbohydrate, protein, or fat diets and of starvation upon the sugar tolerance curves of healthy young men, and I (12) was able to confirm his results completely on similar subjects as regards the effect of fat diets and carbohydrate diets. It may now be taken as securely established that fat diets diminish the sugar tolerance and carbohydrate diets improve it. In addition to this point I was able to show that the fat diets decreased the rate at which a standard dose of crystalline insulin, injected intravenously, depressed the blood sugar whilst carbohydrate diets increased this rate. A correlation thus appeared to exist between a healthy individual's sugar tolerance and his susceptibility to injected insulin and this correlation has since been extended and established further in animals (13). For this reason in the present work the effect of the factor under examination both on the subject's sugar tolerance and on his susceptibility to a standard dose of insulin has always been investigated.

* Beit Memorial Research Fellow

Methods To answer the above questions a glucose tolerance curve, a pH determination and an insulin depression curve were required under each of the conditions stated, namely, when the subject was on a high fat diet, on a high fat diet and taking alkali, on a high carbohydrate diet, and on a high carbohydrate diet and receiving sufficient ammonium chloride to produce an acidosis. This series of experiments was carried through completely in two individuals and partially carried out on a third. The glucose tolerance curve, pH determination, and insulin depression curve each occupied one day, so that the last three days of any particular dietetic regime were occupied in the test experiments. The procedure was the same in both subjects and that for subject V will now be described.

The subject was admitted to the ward on February the 22nd, 1932, and given a high fat diet (carbohydrate 55 g, protein 88 g, fat 202 g). On March the 4th a glucose tolerance curve, on March the 5th a pH determination and on March the 7th insulin depression curve, were obtained.

At 2 p.m. on March the 7th, whilst on the same diet, administration of sodium bicarbonate was commenced and 60 g daily were given in six doses of 10 g at 2 p.m., 7 p.m., 10 p.m., 2 a.m., 7 a.m., 11 a.m. The test experiments were carried out as follows: on March the 16th a glucose tolerance curve, on March the 18th an insulin depression curve, and on March the 19th a pH determination. The administration of alkali was continued throughout the three days of the tests.

At noon on March the 19th the subject was given the high carbohydrate diet (carbohydrate 660 g, protein 90 g, fat 42 g). On March the 30th a glucose tolerance curve, on March the 31st a pH determination, and on April the 1st an insulin depression curve, were determined.

At 2 p.m. on April the 1st ammonium chloride was given and the high carbohydrate diet continued. 15 g daily were given in six doses of 2.5 g at 2 p.m., 7 p.m., 10 p.m., 2 a.m., 7 a.m., 11 a.m. On April the 9th a glucose tolerance curve, on April the 10th a pH determination, and on April the 11th an insulin depression curve, were carried out. The giving of ammonium chloride was continued during the three days occupied by the tests.

When it is desired to compare the pH of the blood under different conditions it is obvious that determinations on blood drawn from peripheral veins are open to grave objections. The composition of such blood must vary considerably with the degree of vaso-dilation in the limb, the activity of the muscle and other local conditions can only fortuitously be the same in any two samples taken at different times. As for our purpose we desired to know the reaction of the blood to which the tissues in general were subjected it is evident that we could only achieve our object by measuring the pH of arterial blood.

chamber The screw clips were re-applied to the rubber tubing and the blood chamber separated from the gas chamber by cutting the tube between the clips

An evacuated sampling tube was then fixed to the upper outlet of the gas chamber The connections were filled with mercury The cocks were then rapidly opened and closed and a sample of gas from the gas chamber thus taken Mercury was run into the sampling tube until there was a slightly positive pressure inside it, and by means of a hypodermic syringe $\frac{1}{2}$ c c $2N.H_2SO_4$ was introduced so as to present solution of CO_2 in the condensed water vapour The tube was then sealed with mercury

A mercury reservoir was connected with the blood container, the whole being under water at $38^\circ C$ The blood chamber was then clamped with the cut rubber tube projecting just over the surface of the water After drying, the projecting cup of rubber tubing was filled with air free liquid paraffin and a 10 c c measuring pipette containing 2 c c of liquid paraffin was pushed into the rubber tube The screw clip was then removed from the tubing and the blood was forced out of the blood chamber by mercury pressure into the pipette, in which it rose under a seal of liquid paraffin The blood was rapidly transferred to a centrifuge tube coated with paraffin wax and surrounded by a water jacket at $38^\circ C$ A further seal of paraffin wax (M.P. $44^\circ C$) was placed over the blood and then the tube in its water jacket was centrifuged for 15 min at 3,500 revolutions Afterwards the paraffin wax sealing the blood was pierced in two places under liquid paraffin The stem of a bulb pipette was then forced down one hole until almost touching the surface of the corpuscles This procedure naturally pushed a seal of liquid paraffin into the pipette By air pressure the plasma was forced into the pipette and then delivered into a clean tube under liquid paraffin When this plasma was required for analysis it was forced by air pressure into the calibrated Ostwald stopcock pipettes

This plasma was analysed in the Van Slyke constant volume gas analysis apparatus following the inventor's technique (18) The various gas mixtures were analyzed in the Haldane apparatus

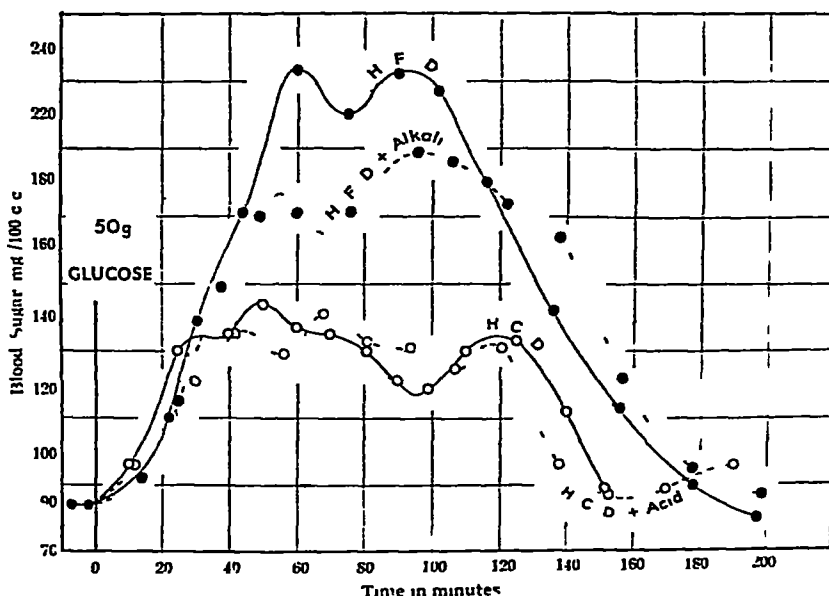


Fig 1 Blood sugar curves obtained after oral administration of 50 g of glucose The curves obtained under the different conditions are distinguished as follows high fat diet H.F.D. high fat diet, plus alkalosis H.F.D. + alkali high carbohydrate diet H.C.D., high carbohydrate diet plus acidosis, H.C.D. + acid

Results In Fig 1 are shown the sugar tolerance curves obtained in the above series of experiments on subject VI It may be noted that it is usual for glycosuria to occur during a sugar tolerance curve on a healthy individual taking a high fat diet, and that as a rule sugar also appears in

Conclusions The pH of the arterial blood of a healthy individual remains the same whether a high fat or a high carbohydrate diet is given. The administration of ammonium chloride, over a period of 10 days, to a subject taking a high carbohydrate diet induces a compensated acidosis, so that the concentration of hydrogen ions in blood is at the upper limit of the normal range, but produces no alterations either in the glucose

TABLE I

Diet	CO ₂ tension of alveolar air (N T P)	CO ₂ content of plasma in mM per L	pH
Subject V			
(1) High fat	43.4	24.90	7.36
(2) High fat + alkali	47.2	29.57	7.40
(3) High carbohydrate	44.0	25.32	7.36
(4) High carbohydrate + acid	41.3	20.4	7.31
Subject VI *			
(1) High carbohydrate	42.0	24.95	7.37
(2) High carbohydrate + acid	38.0	20.69	7.32
Subject VII			
(1) High carbohydrate diet	40.9	23.39	7.36

* The specimens taken on the high fat diet and the high fat diet + alkali were both spoiled through technical mishaps.

tolerance or insulin depression curve from that characteristic of the high carbohydrate diet. The giving of sodium bicarbonate for eleven days to a subject taking a high fat diet induces a compensated alkalosis, the concentration of hydrogen ions in the blood falling to the lower normal limit, but produces no significant alteration in either the glucose tolerance or insulin depression curve from that characteristic of a high fat diet.

It must, however, be understood that it is not suggested that these results exclude the possibility of some change in tolerance, or sensitivity to insulin, being produced by sudden and more extreme variations of pH consequent upon single massive doses of acid or alkali, or that the taking of single large amounts of fat or carbohydrate by a healthy individual, adjusted to an ordinary diet, may not produce a change of pH beyond the normal range. The results do show that the changes in sugar tolerance characteristic of either the high fat or the high carbohydrate diet are unrelated to changes in reaction of the blood.

The influence of ketosis

Graham *et al* (9) suggested that the beneficial effects of high carbohydrate diets in diabetes mellitus, may be due to the effect of these diets in reducing the amounts of ketone bodies produced in the course of metabolism. They think that a ketosis, or alternatively some intermediate metabolic product of which the presence of a ketosis is the indicator, increases the amount of insulin required by the body. Presumably this effect would be brought about by the ketone bodies in some way interfering with the action of the insulin. If this explanation were correct it would obviously have a very important bearing on the functional pathology of diabetes mellitus. I have shown in previous papers (12, 13) that conditions which bring about an impairment in sugar tolerance in a healthy organism also interfere with the action of insulin in depressing the blood sugar. Now a high fat diet will impair the sugar tolerance and interfere with insulin action in a healthy man and it will also in the first days of its administration produce a marked ketosis. As this ketosis is transient, and disappears in the course of a fortnight we have here the opportunity of deciding by direct investigation in healthy man whether the presence or absence of a ketosis impairs sugar tolerance or interferes with insulin action.

Methods and results. The nitro-prusside reaction was used for the detection of aceto-acetic acid in urine. The technique was standardised and it was found that by noting the strength of the colour reaction at the end of 10 minutes a rough quantitative estimation of the amount of the substance present could be made. We classified the reactions as trace, +, ++, and ++++. According to Kennaway (14) this reaction will detect aceto-acetic acid in concentrations of 1 in 200,000. From the subject under investigation 7 urine specimens were obtained daily at the following times: one at mid-night, and one $\frac{1}{2}$ hr before and one 2 hr after breakfast, the mid-day meal and supper. These were each tested for ketone bodies.

The healthy subjects were admitted to the wards in the usual way and given a high fat diet. Within 36 hrs at the latest ketone bodies appeared in the urine and continued to increase in amount up to the end of the first week. After this time, although a diet, containing exactly the same amounts of carbohydrate, protein and fat, was continued, the amount of ketone bodies excreted in the urine began to decrease until during the third week of the diet they had either completely disappeared or were detectable only as an occasional trace in one of the seven daily specimens. Glucose tolerance and insulin depression curves were found to be the same whether they were obtained at the height of the ketosis or when the ketosis was absent.

Fig 2 illustrates this observation. For both glucose tolerance curves the subject was receiving a daily diet composed of carbohydrate 56 g, protein 87 g, fat 255 g. The first tolerance curve was performed when the fat diet had been taken for 11 days. The urine gave a fairly strong

nitro-prusside reaction in all 7 specimens. The second curve was performed 11 days later, the nitro-prusside reaction was negative in all specimens. It will be seen that the sugar tolerance was unchanged.

Subject VI provided data of further interest during the investigation recorded in the previous section. When the first glucose tolerance and insulin depression curves were obtained, after 12 days on the high fat diets, the urine contained only traces of ketone bodies. As soon as alkali was given, along with the high fat diet, ketone bodies were produced in such quantities as to give a maximum nitro-prusside reaction in the urine. This observation is in accord with the recognised influence of an alkalosis in promoting the production of a ketosis (6). The insulin depression curve taken at the end of the period under this regime was unchanged and Fig. 1 shows that this high degree of ketosis did not affect the sugar tolerance adversely.

Objection may be raised to these experiments that the subjects, although receiving the same diet, were not under exactly the same regime when their sugar tolerance and insulin sensitivity were tested. We have made observations on the influence of ketone bodies in nine different subjects. In some of these in order to ensure that the maximum diminution of glucose tolerance and maximum decrease in sensitivity to insulin on the high fat diet had occurred two or more series of tests were carried out at intervals when the subject was receiving the identical foodstuffs each day. In these cases the excretion of ketones diminished as time progressed and yet we could find no correlation between our tests and the degree of ketosis.

These results show that the presence or absence of ketosis has no influence upon either the glucose tolerance or action of insulin in a healthy man. As regards the suggestion that ketonuria is only an indicator of the presence of some unknown interfering substance, it appears to us that if the ketone bodies are indicators of some hypothetical interfering substance then the amount excreted ought to bear some quantitative relation to the amount of interfering substance present—the greater the ketonuria, the greater the amount of the insulin inhibitor. If this is so our objections against the suggestion that the ketone bodies act as substances interfering with insulin action, are equally valid against the suggestion that the substance whose presence they indicate interferes with insulin action.

Conclusion. The presence or absence of a ketosis has no influence upon the sugar tolerance or sensitivity to insulin of healthy men.

The influence of giving liver

In the course of their observations on cases of pernicious anæmia under treatment with liver Blottner and Murphy (4) observed that some of their patients experienced symptoms suggesting hypoglycæmia and that these symptoms occurred when the blood sugar was somewhat lower than normal. They accordingly investigated on normal subjects the effect on the blood sugar of giving a meal containing 20 g. of carbohydrate, 40 g.

of protein, and 35 g of fat, in which on one occasion the protein was made up of red meat on another of raw liver pulp. They reported that the hyperglycemia was lower after the second type of meal than after the first and concluded that liver contains a substance capable of reducing the blood sugar when given by mouth. They applied their results to cases of diabetes mellitus and reported good results coming to the conclusion that 180 g of raw liver pulp produced the same effect as 10 units of insulin. De Pencier, Soskin and Best (7) investigated these claims, but working with dogs could find no evidence in support of them.

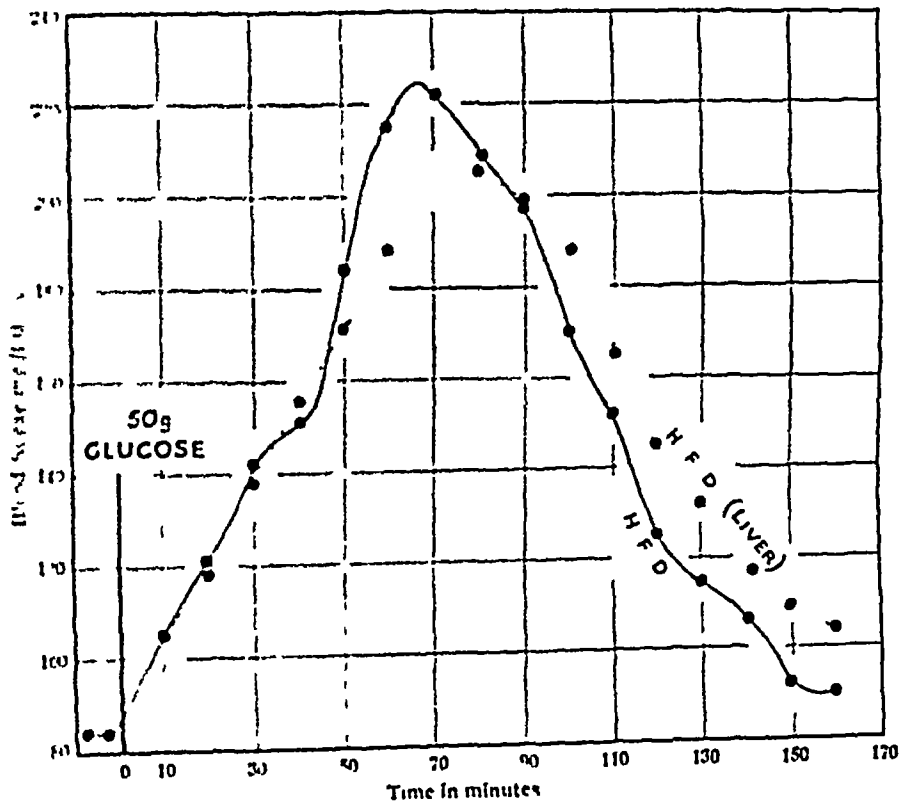


FIG. 2. Blood sugar curves after 50 g of glucose by mouth. That on the ordinary high fat diet is marked H.F.D., whilst that obtained when the subject was receiving a high fat diet containing the same amount of carbohydrate, protein and fat but in which was incorporated 225 g of raw liver daily, is indicated by H.F.D. + Liver.

Methods and results. The subject was admitted to the ward and given the high fat diet (carbohydrate 56 g, protein 87 g, fat 255 g), and 11 days later the sugar tolerance and insulin depression curves were determined. The diet was then adjusted so as to contain 225 g of fresh, raw, liver pulp daily, but the amounts of carbohydrate, protein and fat were kept unchanged. Eleven days later the sugar and insulin tests were carried out. The insulin depression curves were identical and reference to Fig. 2 will show that the glucose tolerance curves on the two occasions were also identical.

During the period of liver feeding the subject experienced no symptoms of hypoglycæmia—with which he was familiar—but he did develop severe headaches—with which he was previously unfamiliar

Conclusion The ingestion of raw liver has no effect upon a healthy subject's sugar tolerance or sensitivity to insulin

The influence of the ingestion of lecithin

In 1932 Best and Hershey (2) showed that the administration of lecithin to depancreatized dogs prevents the fatal hepatic failure which otherwise develops in these animals. This condition is characterised pathologically by the deposition of large amounts of saturated fats in the liver and the beneficial effect of the lecithin appears to be connected with its action in preventing the deposition of this fat. Best, Hershey and Huntsman (3) further showed that the giving of a diet containing much saturated fat to normal rats resulted in the accumulation of this type of fat in the liver, and they demonstrated that if, after this had occurred, lecithin was added to the fat diet the excess of fat disappeared. As the diets which produced a diminution of sugar tolerance in healthy men all contain large amounts of saturated fat it appeared possible that these diets also caused an accumulation of fat in the liver. It occurred to us that the administration of lecithin along with the high fat diet to a normal subject might, by removing the excess of fat from the liver, result in an improvement of the characteristically impaired sugar tolerance.

Method With the help of Professor C. R. Harrington 200 g of dry lecithin were prepared from the yolks of 240 fresh eggs by the method of precipitation with a saturated solution of cadmium chloride in methyl alcohol (15). The final product was a white brittle solid which had an iodine number of 69.4, and a nitrogen content of 1.98%. The substance was thus practically pure lecithin. It should be noted that the preparation was stored in a desiccator and that the weights of lecithin administered to the test subject refer to the dry substance.

The subject was admitted to the ward under the usual routine. He was given the standard high fat diet (carbohydrate 56 g, protein 87 g, fat 255 g). Nine days later a glucose tolerance curve was determined, and two days after this the insulin depression curve was obtained. The diet remaining the same, the oral administration of lecithin was now begun, 25 g being given daily in five doses of 5 g, at 12 p.m., 5 p.m., 10 p.m., 3 a.m., and 8 a.m. Because of its unpleasant taste the substance was given in capsules. After seven days of this treatment the sugar tolerance curve was performed and next day the insulin depression curve was determined. The subject received in all 194 g of dry lecithin. He was now, for a further period, given the high fat diet, but without lecithin, and at the end of 10 days his insulin depression curve was again determined and two days afterwards the sugar tolerance curve obtained.

Every day during the investigation the urine passed in the 24 hours was collected and its phosphate content estimated by the uranium acetate method

Results During the preliminary period on the high fat diet an average of 0.86 g of phosphorus was excreted in the urine daily. With the administration of the lecithin the output of phosphorus began to rise and at the end of 72 hours is reached a level about which it continued to oscillate for the rest of the period of lecithin administration. The average amount of phosphorus in the urine during this period, in which the excretion was steady, was 1.83 g per 24 hours, an increase of 0.97 g. Taking the molecular

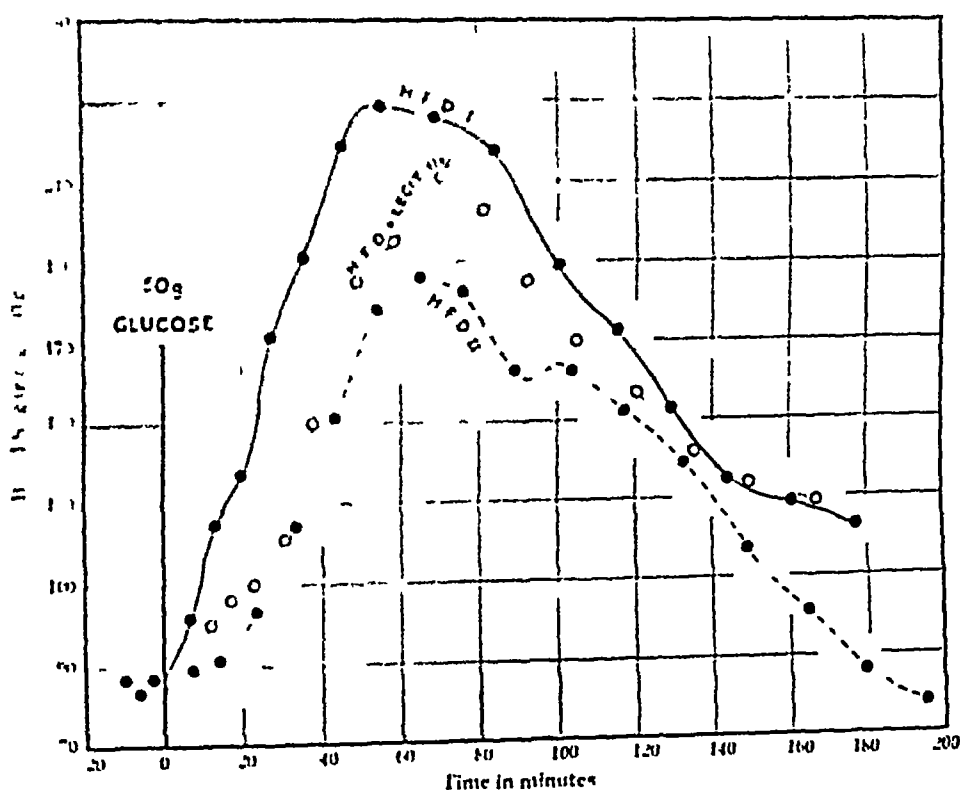


Fig. 3 Blood sugar curves after 50 g of glucose by mouth. The curve on the ordinary high fat diet is distinguished as HI DI, that after the period of administration of lecithin by HI DI + Lecithin, and that performed 10 days after the subject ceased to receive lecithin by HI DI II.

weight of lecithin as 805 it will be seen that 0.97 g of phosphorus are contained in approximately 25 g of lecithin. Thus the whole of the lecithin administered was absorbed from the alimentary canal.

In Fig. 3 are shown the glucose tolerance curves obtained in this investigation. The curve obtained during lecithin administration is slightly lower than that given after the preliminary period of standardisation on the high fat diet. This improvement, however, is insufficiently marked to be unequivocally significant. The interest of this investigation, however,

lies in the third curve, which was obtained ten days after the administration of lecithin had ceased and whilst the subject was continuing to take the high fat diet. The glucose tolerance curve now shows a definite delay in its rise, has a comparatively low peak and at the end of three hours has returned to the fasting level of blood sugar. In seven curves obtained from this subject, whilst taking this same diet, no other showed such a low peak or rapid return to normal levels. Comparing this result with the preliminary curve on the high fat diet we are of the opinion that a slight but definite improvement in tolerance is indicated. Considering the large amount of lecithin given this result is not striking and shows that the administration of lecithin does not produce an effect comparable with that of giving a high carbohydrate diet. The slight delayed improvement in tolerance, however, may be of some significance as indicating that the giving of lecithin over a longer period and in amounts greater even than the above excessive dose, might produce some increase in tolerance.

The insulin depression curves unfortunately are incomplete as the specimens taken for the curve obtained during the preliminary high fat period were spoilt in analysis. However, the curve performed in the lecithin period falls slightly less rapidly than that taken twelve days afterwards when the subject was receiving the fat diet alone. The fall in both curves is of the slow type characteristic of the high fat diet.

Conclusion The oral ingestion of 25 g of pure lecithin daily produced little or no improvement in the sugar tolerance of a healthy man receiving a high fat diet. A small delayed improvement in tolerance appeared to have occurred ten days after the cessation of the lecithin administration.

SUMMARY

1 It has been demonstrated in normal human subjects that the diminished glucose tolerance and impaired sensitivity to insulin observed when the subject is taking a high fat diet do not depend upon a change in the pH of the blood to the acid side, and that the improved glucose tolerance and increased sensitivity to insulin found in subjects receiving a high carbohydrate diet are unassociated with a change in the pH of the blood to the alkaline side.

The reaction of the blood was found to be the same on either diet.

It has further been shown that the production of a compensated alkalosis in a subject on a high fat diet results in no improvement either of the impaired sugar tolerance or diminished sensitivity to insulin and that the presence of a compensated acidosis has no deleterious effect upon the increased sugar tolerance and insulin sensitivity characteristic of the high carbohydrate regime.

2 In normal men the presence of a ketosis has no effect either upon the glucose tolerance or the sensitivity to insulin.

3 The administration of raw liver to a subject balanced on a high fat diet produced no change in glucose tolerance or insulin sensitivity

4 The daily oral ingestion of 25 g of lecithin for a period of one week, to a subject standardised on a high fat diet, caused little or no change in the glucose tolerance. Ten days after cessation of the lecithin administration a small delayed improvement in tolerance appeared to have occurred, although the subject continued to receive the same high fat diet

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THE RELATIONSHIP BETWEEN THE TOTAL OSMOTIC PRESSURES OF PLASMA AND OEDEMA FLUID IN MAN

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Introduction

THIS paper is concerned with the measurements of osmotic pressure which we have made on samples of plasma and of oedema fluid in man. Our results are discussed in relation to the hypothesis that oedema fluid is a simple ultrafiltrate of plasma and that the walls of the minute vessels behave like an inert dialysing membrane which resists the passage of red cells and colloids but permits the free diffusion of water and crystalloids. If oedema fluid is an ultrafiltrate of plasma then the total molecular concentration of crystalloid should be equal in plasma and oedema fluid, and therefore the difference between the total osmotic pressures of plasma and oedema fluid should equal the difference between their colloid osmotic pressures.

The colloid osmotic pressure of plasma is, however, less than 1% of the total osmotic pressure, and may be of the same order or less than the errors encountered in the usual freezing point methods for determining the total osmotic pressure. The colloid osmotic pressure of oedema fluid is usually less than one-seventh of the colloid osmotic pressure of normal plasma.

Hill's vapour pressure method which we have used for determining osmotic pressures is sensitive to changes in osmotic pressure which are of smaller magnitude than the colloid osmotic pressure of normal plasma and has in addition to its greater accuracy the advantages over other methods that measurements are made at a temperature nearer to the body temperature, that the effects of changing the gaseous tension of the plasma and oedema fluid are more readily studied, and that it may be used differentially.

Most of the workers interested in the osmotic relationship of blood and pathological effusions have compared the freezing point depression of whole blood or plasma with that of pleural effusion, ascitic fluid or hydrocele fluid and few only have included measurements on oedema fluid.

Observers usually agree that within the limits of error of the methods used the total osmotic pressures of whole blood or plasma and effusions are

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equal. Most have ignored the fact that a fall in CO_2 tension causes a decrease in the osmotic pressure of whole blood. This effect of CO_2 was observed by Bottazzi (2) [since by others (6) (3)] Gollwitzer-Meier (5) who paid attention to this effect upon osmotic pressure of changing the CO_2 tension found the osmotic pressures of oedema fluid and plasma equal. She criticised Beckmann (1) who seems to have neglected the CO_2 effect and interpreted the differences which he consequently observed in the osmotic pressures as evidence of secretion by the walls of minute blood vessels.

Galotti (4) produced oedematous effusions experimentally in dogs by intravenous injections of hypertonic saline or glucose after ligation of the crural vein. His results were especially interesting in that the osmotic pressures of plasma and oedema fluid were equal despite the abnormal elevation of the osmotic pressure of plasma.

Method

Samples of oedema fluid were obtained by inserting the point of a hollow needle of large bore into the subcutaneous tissues. The oedema fluid was allowed to flow directly into a test tube. In order to prevent evaporation a plug of cotton wool was inserted into the mouth of the test tube.

Samples of blood were removed with a minimum of congestion from the antecubital veins and precautions were taken to prevent the loss of blood gases. The record syringe which received the blood was previously lubricated with liquid paraffin and the blood was transferred without delay to a centrifuge tube provided with a well-fitted rubber stopper. Before inserting the stopper any air above the blood was mostly replaced by the observer's alveolar air which was breathed into the tube. Usually, however, the volume of blood which was removed sufficed to fill the centrifuge tube. There was thought to be no appreciable loss of blood gases prior to separation of the plasma. Fibrin coagulation was delayed by heparin or alternatively the blood was debrinated using glass beads.

The vapour pressure measurements were made by the method of Hill (7). In this method 2 small pieces of filter paper are soaked in solutions of a known and unknown osmotic pressure respectively. The temperature changes which are produced by the evaporation of the two solutions held in the filter papers are compared by means of a special thermopile upon which the 2 filter papers are laid. The principle is similar to that of the wet and dry bulb thermometer. The error of the method is about $\frac{1}{2}\%$ of the total osmotic pressure. The measurements are made either in air or in 5% CO_2 in oxygen.

Results

A comparison of the total osmotic pressures of oedema fluid and plasma, the measurements being made in an atmosphere of air. In our early experiments we compared the vapour pressures of the plasma and oedema fluid in an atmosphere of air. We used for this estimation plasma which was separated

from its red cells at the CO₂ tension of the venous blood sample. We thought from the work of Margaria (8) that once the red cells were separated from the plasma the *relationship* between the osmotic pressures of plasma and oedema fluid would not be changed by exposing the two liquids to another CO₂ tension.

When we made our measurements in air we found that the total osmotic pressures of plasma and oedema fluid were nearly equal but that the oedema fluid had, if anything, a slightly higher value, the average difference being about 0.002 g NaCl per 100 g H₂O (approximately $\frac{1}{4}$ th % of the total osmotic pressure). This result was surprising for the total osmotic pressure of the oedema fluid should have been a little less than the total osmotic pressure of the plasma, differing from it by about 0.007 g NaCl per 100 g H₂O, which is the average colloid osmotic pressure of the plasma expressed in

TABLE I

The difference in the osmotic pressures of oedema fluid, plasma and whole blood when measured in 5% CO₂ and in air

	Oedema fluid		Plasma or serum		Whole blood	
	in	Diff	in	Diff	in	Diff
A	5% CO ₂	0 010	5% CO ₂	0 018	5% CO ₂	0 025
	0 884 } 0 885 0 886 } % NaCl		0 893 } 0 895 0 897 } % NaCl		0 887 } 0 890 0 892 } % NaCl	
	Air		Air		Air	
	0 875 } 0 875 0 875 }		0 876 } 0 877 0 878 }		0 863 } 0 865 0 866 }	
B	5% CO ₂	0 010	5% CO ₂	0 017	5% CO ₂	0 027
	0 816 } 0 818 0 819 }		0 834 } 0 835 0 836 }		0 842 } 0 843 0 843 }	
	Air		Air		Air	
	0 807 } 0 808 0 809 }		0 818 } 0 818 0 818 }		0 814 } 0 816 0 818 }	
C	5% CO ₂	0 018	5% CO ₂	0 029	5% CO ₂	0 040
	0 903 } 0 903 0 904 }		0 909 } 0 910 0 910 }		0 914 } 0 915 0 917 }	
	Air		Air		Air	
	0 885 } 0 885 0 884 }		0 881 } 0 881 0 881 }		0 875 } 0 875 0 874 }	
D	5% CO ₂	0 011	5% CO ₂	0 015	5% CO ₂	0 036
	0 876 } 0 877 0 878 }		0 888 } 0 888 0 889 }		0 883 } 0 884 0 884 }	
	Air		Air		Air	
	0 865 } 0 866 0 867 }		0 871 } 0 873 0 875 }		0 847 } 0 848 0 849 }	
Average		0 012	0 020		0 032	

All measurements are expressed differentially with respect to saline. Hence the results show the relative capacities of oedema fluid, plasma and whole blood to take up CO₂ compared with saline.

TABLE II
The relationship between the total osmotic pressures of oedema fluid and plasma

	Oedema fluid > plasma Measured in air	Oedema fluid > plasma Measured in 5% CO ₂	Oedema fluid > whole blood Measured in 5% CO ₂
A	0.002 % NaCl	— 0.010 % NaCl	— 0.005 % NaCl
B	0.010	— 0.017	— 0.025
C	0.011	— 0.007	— 0.012
D	0.007	— 0.011	— 0.007
Average	0.004	0.011	— 0.012

terms of an isotonic sodium chloride solution. In investigating the effects of change in the CO₂ tension upon the total osmotic pressures of oedema fluid, plasma and whole blood we discovered the explanation of this.

The effects of changes in the carbon dioxide tension on the total osmotic pressure of oedema fluid, plasma and whole blood. It is clear from Table I that if we take samples of oedema fluid and plasma which are in osmotic equilibrium with each other at a certain concentration of CO₂ and then bring both liquids into equilibrium with air, the plasma suffers a greater fall in osmotic pressure than the oedema fluid, the average difference in these four experiments being equivalent to 0.008 g NaCl per 100 g of water. There is little doubt that this is due to a greater loss of CO₂ from the plasma. The relationship between the osmotic pressures of plasma and oedema fluid samples depends therefore upon the CO₂ tension of the atmosphere in which they are measured (Table II). In regard to gaseous tension the measurements in 5% CO₂ are a closer approximation to conditions in the body than are measurements in air.

In order to make the differences in the osmotic pressures of oedema fluid and plasma when measured in air, comparable with the differences when measured in 5 per cent CO₂ we must add 0.008 to those differences which were measured in air.

The equality of the total osmotic pressures of oedema fluid and plasma when measured in air, is due to the coincidence that the contribution to osmotic pressure of the plasma proteins is neutralised by the effect upon osmotic pressure of the loss of CO₂ (which loss of CO₂ takes place to a greater degree from the plasma than from the oedema fluid when both are exposed to air).

A comparison of the total osmotic pressures of oedema fluid and plasma upon the basis of measurements made in or corrected to an atmosphere of 5% CO₂. Thirteen comparisons were made which seemed technically perfect. There were 3 cases of congestive heart failure, 5 cases with hypoproteinaemia, 2 cases with oedema of the legs starting late in pregnancy, 1 case of unknown

origin following pregnancy, 1 case of thrombosis of the femoral vein and 1 case of unknown origin. Of the 5 cases with hypoproteinaemia 1 was nutritional and 4 had nephritis. In 12 cases the patients were at rest in bed, in the remaining case the patient walked to hospital but rested for about $1\frac{1}{2}$ hours before the sample was taken.

In the 13 experiments the differences between the total osmotic pressures of oedema fluid and plasma when measured in or corrected to 5% CO_2 tension were (-0.026), -0.017 , -0.011 , -0.010 , -0.007 , -0.006 , -0.005 , -0.004 , -0.003 , -0.0025 , $+0.0005$, $+0.0025$, $+0.004$. The figures in italics are those obtained by comparing the total osmotic pressures of oedema fluid and plasma in air and then correcting to 5% CO_2 tension by the addition of 0.008 to the total osmotic pressure of plasma. The average (omitting the one obviously aberrant result) is -0.0058 g NaCl per 100 g water.

Fig 1 shows that although the total osmotic pressures of oedema fluid and plasma vary greatly, the difference between them is approximately the same in each case. It seems therefore that this relationship is independent of the cause of the oedema.

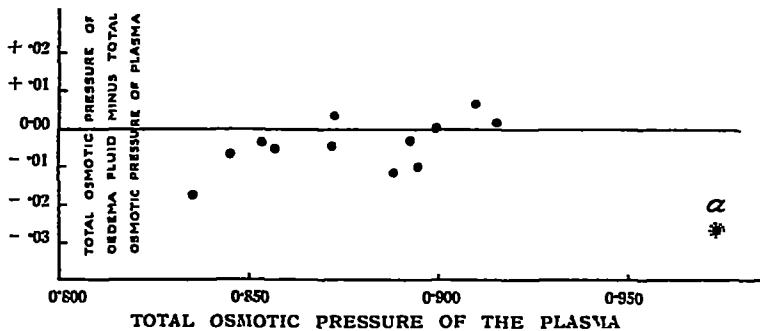


Fig 1 Changes in the total osmotic pressure of plasma are accompanied by similar changes in the total osmotic pressure of oedema fluid. *a* = an aberrant result which is omitted from the average.

If oedema fluid is a simple filtrate of plasma then the average difference between the total osmotic pressures of oedema fluid and plasma (0.0058) should equal the average protein osmotic pressure of the plasma. Now in 5 subjects out of the 13 there was reason to expect the presence of a subnormal percentage of protein in the plasma. In these 5 subjects the magnitude of the protein osmotic pressure was gauged from estimations of the protein percentage of the plasma and the data supplied by Van Slyke (9) (Average of the 5 calculated osmotic pressures 0.004% NaCl). In the remaining 8 subjects with oedema due to congestive heart failure, venous thrombosis, etc., the protein osmotic pressure of the plasma was assumed to be normal (0.007% NaCl). The average of these 13 osmotic pressures is 0.0063, and allowing for the approximate nature of the calculations the true average osmotic pressure must lie between 0.005 and 0.0065. This is a

There is therefore good reason to believe that if time is allowed for diffusion the crystalloids of the œdema fluid and of the plasma will come into osmotic equilibration with each other

The significance of the relationship between the crystalloidal osmotic pressure of œdema fluid and plasma Starling supported the view that in œdema formation the minute blood vessels permit the diffusion of water and crystalloids but resist the diffusion of colloids. He thought that the forces responsible for the formation of œdema fluid and for its removal through blood vessels are mainly the mechanical pressures in and around the blood vessels and the colloid osmotic pressure of the plasma

This view assumes that all crystalloid ions and molecules pass freely through the blood vessels, for an asymmetry in the distribution of crystalloids would affect the relationship between the osmotic pressures of plasma and œdema fluid, and so influence the passage of fluid through blood vessels. In plasma the osmotic pressure of the crystalloids is about 5000 mm of mercury and of the colloids about 30 mm of mercury. Hence a 1% asymmetry in the distribution of crystalloids causes a change in osmotic pressure which is greater than the entire colloid osmotic pressure

We have found that the crystalloidal osmotic pressures of plasma and œdema fluid are equal and this is best explained if we assume that the walls of the minute blood vessels are freely permeable to water. This view is consistent with but is not proof of the hypothesis that œdema fluid is a simple filtrate of plasma. It may be for example that certain crystalloids are concentrated in or withheld from the œdema fluid by a secretory process involving the performance of work. It is not suggested that such secretion is likely, but if there is secretion our results indicate that the minute vessels are nevertheless unable to prevent the diffusion of water, so that osmotic if not chemical equilibrium of plasma and œdema fluid is restored

Proof that the walls of the minute vessels lack secretory function involves a demonstration that the distribution of all ions and molecules between œdema fluid and plasma is the same as if these liquids were separated by an inert dialysing membrane. Much has been done by other workers in this field and there is little doubt that within the range of experimental error the distribution of chlorine, bicarbonate, sodium, calcium and urea is what would be expected from a filtration hypothesis. A few investigations of other ions are recorded with results that are less conclusive but which cannot be regarded at present as evidence against this view

SUMMARY

1 In man the total osmotic pressures of plasma and œdema fluid have been compared by using Hill's vapour pressure method

2 With decrease in carbon dioxide tension the total osmotic pressure decreases more in whole blood than in plasma and more in plasma than in œdema fluid. Therefore, the relationship experimentally found between

the total osmotic pressures of plasma and oedema fluid depends upon the carbon dioxide tension at which the plasma is separated from the red cells, and upon the carbon dioxide tension at which the comparison of the osmotic pressures of plasma and oedema fluid is made

1. At 5% carbon dioxide tension the average total osmotic pressures of oedema fluid and plasma differ by an amount equal to the colloid osmotic pressure of the plasma. Thus the average crystalloidal osmotic pressures of plasma and oedema fluid are equal at a CO_2 tension approximating to that of the body.

2. Despite wide individual variations in the crystalloidal osmotic pressure of plasma from patients with various forms of oedema, it appears that the crystalloidal osmotic pressure of each individual sample of oedema fluid will be equal to that of the plasma from which it was formed, provided time is allowed for the diffusion of water (and probably also of crystalloids) to smooth out the inequalities which may be caused by a temporary excess of metabolites in either fluid.

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THE NATURE OF MYXCEDEMA *

By F B BYROM †

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THE dehydrating properties of thyroid preparations have been recognised ever since Hurry Fenwick (10) in 1891 reported that a myxœdematous patient into whom he had attempted to graft sheep's thyroid passed large quantities of urine after the operation. It is equally well known that thyroxine depletes the protein stores of the body. Two questions raised by these facts have so far remained unanswered, namely (a) Is the lost fluid derived from the intracellular or the extracellular compartments, or from both? and (b) Is it a consequence of the destruction of suspended protein? In the present paper an attempt is made to provide answers to these questions, which in turn throw some light on the nature of myxœdematous swellings. The principles employed have been described in a previous paper (4), cellular and extracellular fluid losses having been calculated from the loss (that is, excess of output over intake) respectively of potassium and sodium by the method of Gamble (12), and depletion of body protein from the nitrogen balance.

The subjects of the investigation were several patients suffering from myxœdema, together with one normal control subject—a healthy unemployed man of 35,—who were given large intravenous doses of thyroxine freshly dissolved in small quantities of normal saline. In order to answer the first question it is necessary to consider the results obtained only in a qualitative sense. The second question on the other hand, requires quantitative comparison of the losses of protein and body fluid. The error attached to clinical determination of mineral balance is often unavoidably high and always incalculable and the difficulties are increased in dealing with myxœdematous subjects, who co-operate poorly. Apart from inevitable variations in the intake of nitrogen and potassium, the most important source of error lies in sweating. Considerable quantities of sodium can be lost in perspiration and estimates of extracellular fluid balance are always subject to an unknown positive bias. Concerning the amount of potassium which may be lost by sweating there is some uncertainty. K N Moss (22) found large quantities of this base in sweat,

* Communicated to the Medical Research Society, London, May, 1933.

† Working as Beit Memorial Research Fellow.

but this may have been due to the fact that sweat collected for analysis may be heavily contaminated with epidermal debris. On general biological

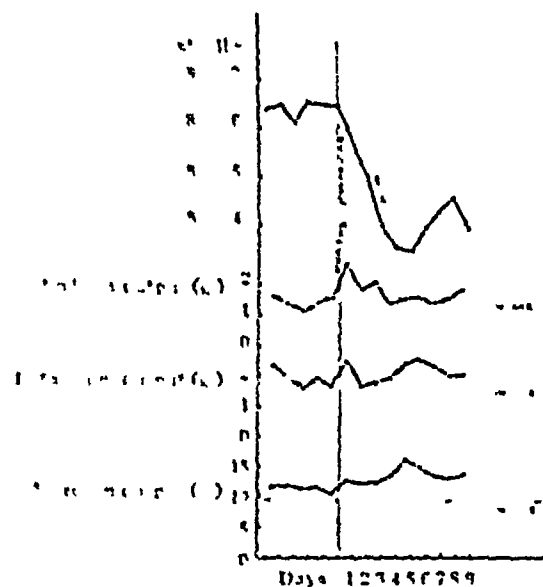


Fig. 1. Effect of 7 m thyroxine on the excretion of sodium, potassium and nitrogen in a normal subject (1 spt. 2)

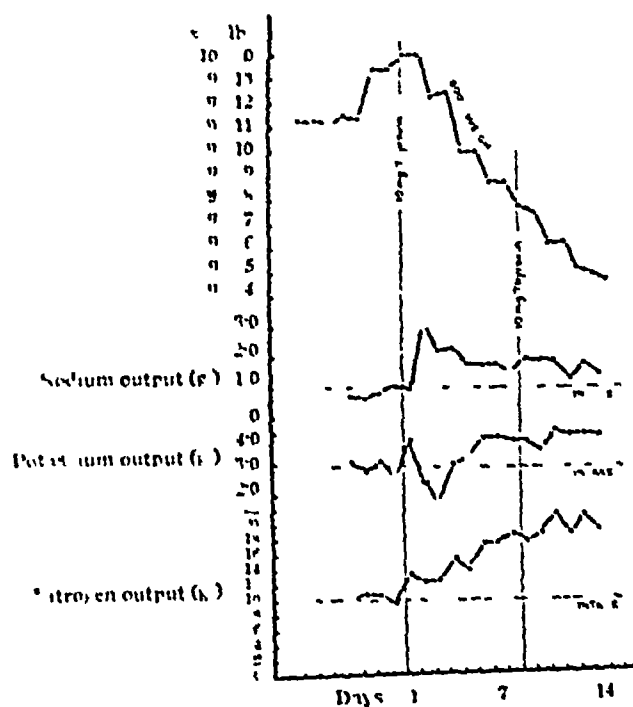


Fig. 2. Effect of thyroxine on excretion of sodium, potassium and nitrogen in a case of myxoedema (1 spts. 1 and 5)

grounds it seems probable that sweating is a function of the extracellular fluids and the work of Fishberg and Bierman (11) and Dill and his associates (7) suggests that the potassium content of sweat does not exceed that of blood plasma. If so, estimates of cellular fluid balance derived from measurements of potassium exchange should not be disturbed by moderate sweating. A further source of error lies in the fact that the potassium and nitrogen content of faeces are too large to be ignored. However, in extremely constipated subjects it is often impossible to collect faeces without using purgatives, which are undesirable in studying fluid metabolism, and in such circumstances it is sometimes permissible to presume a constant rate of faecal loss. The precautions taken to minimise the above errors have been as follows. The subjects were confined to separate rooms in the metabolism ward. Baths were not allowed and every effort was made to minimise sweating. The diets used were fixed and weighed, consisting of boiled eggs, grapefruit, milk, lean meat, orange juice, cane sugar, salt-free butter, and biscuits. The meat was cut from the centre of a roast joint. The biscuits were made from flour and distilled water. No salt was used in cooking, the sodium deficiency of the diet being corrected by a measured volume of sodium chloride solution of known strength. A measured amount of distilled water (1,300 c.c.) was allowed each day. Duplicate diets were dried and analysed for N, Na and K from time to time, butter and sugar being analysed separately. Urine was collected over thymol in 24 hour periods and was mixed, measured and stored for analysis in a refrigerator. Stools were mixed with thymol, acidified with HCl and afterwards pooled, dried and pulverised for analysis, the collection periods being marked with carmine capsules. The small amount of nitrogen in the carmine was ignored. Purgatives were not permitted. For mineral analysis stools and food were ashed in silica beakers in a muffle furnace below red heat. The analytical methods used have been mentioned elsewhere (4).

The effect of thyroid extracts on the excretion of sodium and potassium and of the acid radicals Cl and PO_4 which usually accompany them has been studied by several workers but with singularly discordant results. Boothby and his associates (1, 5) found no consistent change in the excretion of either base in either normal or myxœdematous subjects after large intravenous doses of thyroxine. Ord and White (25) also reported that no increase in the excretion of Cl or PO_4 occurred during the treatment of myxœdema. On the other hand Schttenhelm and Eisler (28) and Gollwitzer-Meier and Brocker (13) have described a loss of sodium but not of potassium, while Nishimoto (23) claims that in normal dogs the excretion of Na, K, Cl , and PO_4 is all increased by thyroid extracts. It would be a remarkable exception to a general rule if thyroxine were capable of causing gross loss of body water without parallel loss of electrolytes, and these divergent findings are no doubt due to the errors mentioned above.

Results (qualitative)

The effect of thyroxine on the fluid and protein reserves of the body is shown in Figs 1 and 2. In these diagrams a rise or fall of the potassium excretion curve above or below the base line representing intake may be interpreted as a loss or gain respectively of cellular fluid. Similarly the excretion curves of sodium and nitrogen may be taken as indices of gain or loss of extracellular fluid and protein by the body.

Normal subject. It is shown in Fig. 1 that the dehydration caused by thyroxine involves both compartments of the body fluids. The loss of extracellular fluid is greatest within 24 hours of the injection and is arrested after three days. During this period the subject lost weight rapidly and his output of urine was increased. The response of the intracellular fluids to thyroxine is more complex. On the day of the injection there is a decided loss of potassium, but on the second and third days the excretion falls back to the previous level. No explanation will be offered of this initial loss of intracellular fluid. The balance then enters a second negative phase which persists until the end of the period of observation.

Myxardoma. In this, the sequence of events is similar (Fig. 2). The extracellular fluid loss is greatest at the outset, but it persists for a longer period than in the normal subject. The intracellular fluid balance also displays the same initial negative phase, which is followed by a phase of retention during which the loss is made good, and then by a more prolonged second negative phase. After a second dose of thyroxine, eight days after the first, there follows an even greater loss of cellular fluid, but a relatively smaller additional loss of extracellular fluid.

The reverse process of recovery from the effect of thyroid medication is illustrated by a third case (Fig. 3). This patient was suffering from gross myxardoma and for a period of four weeks prior to the experiment had received three grains of desiccated thyroid daily. On admission to the metabolism ward the latter was suspended and observations were begun immediately. It will be seen that the body weight falls steeply until, after a loss of three kilograms, equilibrium is reached on the eighth day. The volume of urine excreted during this period was abnormally high and the simultaneous loss of sodium indicates that the fall in weight is largely due to loss of extracellular fluid, for which the previous thyroid medication was presumably responsible. After the eighth day reaction sets in rather abruptly. The body weight begins to rise again, the output of sodium falls below the intake, and the extracellular fluid reservoirs are steadily replenished. During this period the output of urine was abnormally low. Reaccumulation of the lost protein and cellular fluid is a more leisurely process. During the first twelve days the excretion curves of nitrogen and potassium remain at steady levels which approximate to the respective intakes. The loss of protein and cellular water which

presumably occurred during the previous treatment has evidently been followed by a state of equilibrium at a subnormal level of storage. After the twelfth day a phase of retention is observed to begin, the excretion curves of potassium and nitrogen falling together and running parallel courses until about the twentieth day and suggesting that the normal intracellular stores of protein fluid are being simultaneously replenished.

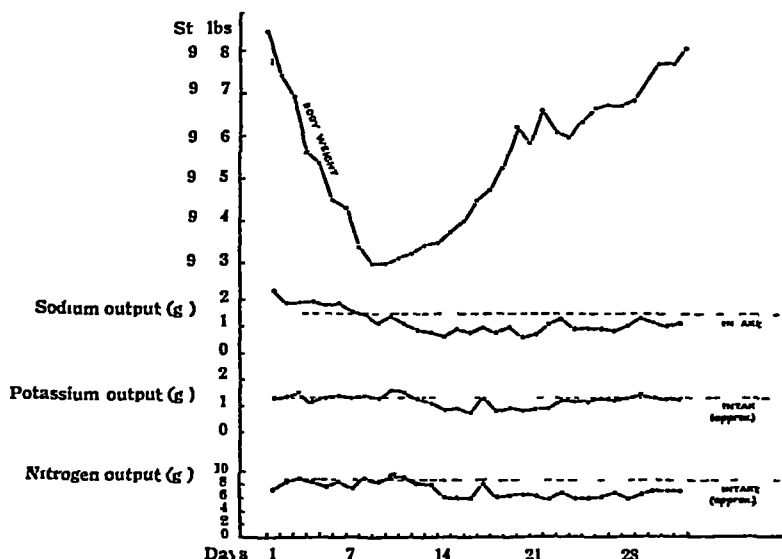


Fig 3 Urinary excretion of sodium, potassium and nitrogen after suspension of thyroid medication in a case of myxœdema

Between the twentieth and the twenty-third days, however, an interesting difference is observed. The potassium excretion rises to attain its previous level of equilibrium, suggesting that the intracellular fluid loss has been made good, while the nitrogen output remains at a low level, suggesting that protein + water is now accumulating in some extracellular site. Viewed qualitatively, then, the above results indicate that in both normal and myxœdematous subjects thyroxine causes depletion of both compartments of the body fluids and the first question is satisfactorily answered.

Results (quantitative)

Since the second question raised above has a direct bearing on the nature of myxœdema, it will be convenient here to outline the scope of the latter problem.

The term myxœdema was applied by Ord (24) to the peculiar subcutaneous swellings of adult hypothyroidism because he found in the tissues of his first case a shmy colloid possessing the chemical characters of a mucoprotein. His results were confirmed by Harley (17), but some

years later doubt was cast on them by Halliburton (14), who was unable to demonstrate any consistent excess of mucin in tissues derived from several cases of myxœdema. At the same time, however, he recovered considerable quantities of mucin from the bodies of animals, the thyroid glands of which had been excised by Victor Horsley. Halliburton's negative findings in human myxœdema were endorsed by Hun and Prudden (19) and later by Bourneville (2) and, although they may have been due to overfixation of the tissues in spirit before analysis, the fact remains that after a lapse of nearly half a century a widespread uncertainty exists about the exact nature of myxœdema. MacCallum (21), for instance, writes in 1932: "There is said to be an accumulation of bluish-staining material here (in the deeper layers of the skin) which was thought to have* a mucoid character" and more recently Harington (16) refers to "this supposed accumulation of mucin" and also states (*loc cit* p. 20) that the signs of myxœdema "may all be explained in terms of reduced metabolism: thus, there is an accumulation of fat—, implying, apparently, that the subcutaneous swellings are composed simply of fat. It will be shown later that apart from the fact that myxœdematous subjects are not conspicuously obese there are serious objections to this simple quantitative conception of myxœdema."

Direct analysis having yielded such equivocal conclusions, it is still possible to approach the problem through indirect channels. In recent years Boothby and his associates (1) have attempted to do so. They measured the urinary excretion of nitrogen in one normal and two myxœdematous subjects after thyroxine and found that the ratio of nitrogen to water (i.e., body weight) lost was identical, namely 1.920, and 1.99%. Boothby concluded "that the œdema of myxœdema is an albuminous colloid fluid with a nitrogen:water ratio higher than the accepted average of 1.1% for human blood serum, and identical with that of egg-white which contains 2% of nitrogen, and definitely less than that of muscle which contains over 3%. In the myxœdematous subject there is an excess of such albuminous fluid as compared with a normal individual and the œdema of myxœdema corresponds apparently to an increase in the reserve or deposit protein." In other words, myxœdema is simply a quantitative error of metabolism—a plethora of protein. This interpretation of Boothby's data would be legitimate only if the protein reserves of the body were uniformly distributed between the two primary fluid compartments. This is far from being the case for in the normal subject the protein stores are confined within the boundaries of the cell wall, the extracellular fluids being in comparison, relatively protein-free. Consequently quantitative comparisons of protein and water losses are not permissible unless the source of the lost fluid is known. In Boothby's control subject, for instance, the nitrogen:water ratio of 2% is as he

* The italics are mine

points out, considerably lower than that of protoplasm (about 4.5%). He infers from this the existence, in the normal subject, of a distinct reserve of "deposit" protein containing at least 43 and perhaps as much as 215 g of protein nitrogen. The low nitrogen water ratio, however, could be more simply explained on the assumption that some of the lost water included in the denominator had been derived from protein free extracellular fluid. Boothby's definition of myxœdema is therefore not justified by the data which he presents. The question at issue in myxœdema is not simply whether there is or is not an excess of protein in the tissue. It is equally important to determine where the excess, if any, is accommodated. It has often been suggested (1, 30) that the deposits fail to pit on pressure because the œdema is largely intracellular. This suggestion is hardly warranted by the morbid anatomy of the disease. The swellings are found, not in cellular tissues such as the muscles and viscera, but in those parts of the body where cells are fewest, and the microscope shows that the excess fluid is extracellular as in ordinary œdema.

Is the doughy character of myxœdema swellings due to the presence of protein in this normally almost protein-free extracellular fluid? If so, it would be expected that when the protein is dispersed by thyroxine a considerable amount of the extracellular fluid which holds this protein in colloidal suspension would be set free from physical combination and excreted, whereas in the normal subject the lost fluid, if any, would be derived from the intracellular compartment, to which the normal protein stores are restricted.

The present results may now be considered in the light of this argument. The estimated quantities of Na, K and N lost by the various subjects are collected in Table I. In Table II these estimates have been translated into extracellular fluid, cellular fluid and protein, and in Fig. 4 the latter are illustrated graphically. In experiments Nos. 1, 2 and 3, the losses represent the difference between output in urine + faeces, and intake as determined by analysis of diet. In experiment 3 the subject rejected several items of the diet and approximate corrections were applied. In the remaining experiments (Nos. 4 and 5) the subject was obstinately constipated throughout. She was kept on a fixed diet for eight days before thyroxine was given, by which time the urinary excretion of Na, K and N had attained constant levels. These levels were used as bases from which to estimate gain or loss from the body, a constant rate of faecal loss being presumed.

Exact quantitative interpretation of such data is impossible in view of the possible errors already mentioned. Subject to confirmation, however, they seem to indicate certain gross differences between the response of normal myxœdematous subjects to thyroxine. These differences are—(Fig. 4)

TABLE I

Approximate amounts of sodium, potassium and nitrogen lost from the body after thyroxine

Expt No	Case	Period of observation	Dose of thyroxine	Sodium loss (g)	Potassium loss (g)	Nitrogen loss (g)
1	Normal subject	10 days	7 mg	1.53	4.60	53.0
2	Normal subject	9 days	7 mg	2.10	3.81	36.7
3	Myxoedema	10 days	7 mg	7.39	0.73	44.5
4	Myxoedema	8 days	10 mg	0.27	2.33	40.5
5	Myxoedema (exam case, second dose)	6 days	10 mg	5.63	5.77	56.1

TABLE II

*Approximate amounts of extracellular and intracellular fluid and of protein lost from the body after thyroxine**(Calculated from the data in Table I)*

Expt No	Case	Loss of body weight (g)	Extracellular fluid loss (g) ($\text{Na}^+ - 0.425\text{K}^+$ 0.118)	Intracellular fluid loss (g) ($\text{K}^+ - 0.017\text{Na}^+$ 0.112)	Protein loss (g) ($\text{N} \times 6.25$)
1	Normal subject	2020	110	1050	332
2	Normal subject	1140	360	860	230
3	Myxoedema	1400	2120	120	276
4	Myxoedema	2100	2550	175	253
5	Myxoedema (second dose)	1700	1220	1200	350

* Expressed as milli equivalents

- (1) That the total and the extracellular fluid losses are greater in myxœdematous patients than in the normal subject (the greater loss of body weight confirms this inference), and
- (2) That the intracellular loss is less

It will be observed that the nitrogen losses, on the other hand, show no consistent differences in the various experiments. Several interpretations of these differences in response to thyroxine are possible, but the most reasonable one is that there is in myxœdema an abnormal extracellular collection of protein + water, towards which the effect of thyroxine is specifically diverted from the normal intracellular stores. It will be noticed (Fig 4, Expt 5) that when a second dose of thyroxine is given

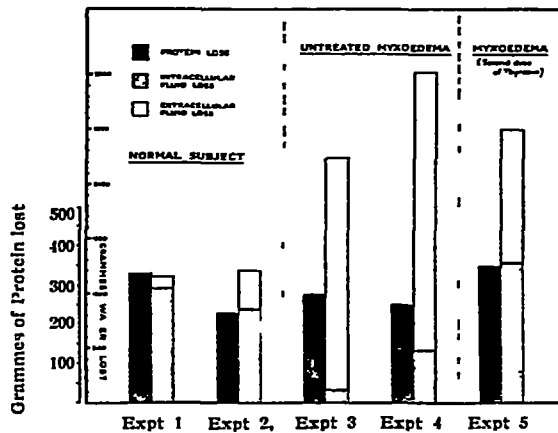


Fig 4 Relative amounts of protein, cellular fluid, and extracellular fluid lost by normal and myxœdematous subjects after thyroxine. Constructed from data in Table 2 and scaled to conform with the protein : water ratio of normal protoplasm, i.e., 2S : 100

six days after the first, the response more closely resembles that obtained in the normal subject. This suggests that the abnormal extracellular deposits have been largely dispersed by the first dose of thyroxine and that the brunt of the second dose is borne by the normal cellular reserves. Implicit in the above reasoning is the assumption that the fluid loss observed is a consequence of destruction of suspended protein, and the further corollary that the effect of thyroxine in the normal subject amounts to piecemeal demolition of protoplasm to furnish protein for fuel, exactly as occurs in starvation (12). Neither of these assumptions, however, is theoretically improbable.

Before proceeding to consider the significance of these conclusions it remains to decide whether the abnormal protein in myxœdema is accommodated within or outside the blood vessels. This question has been answered by simultaneous measurements of the protein content and total volume of the blood plasma immediately before and ten days after the injection of thyroxine (7 mg) into another myxœdematous

patient * During this period the total volume of the plasma rose from 2,320 c.c. to 2,670 c.c., while its protein content fell from 7.72 to 7.05%. Consequently the total amount of protein in the plasma rose from 179 to 188 g. This apparent gain of 9 grammes of protein (1.5 g. of nitrogen) is negligible and could easily be covered by the experimental error of the vital red method.

The abnormal protein in myxœdema is therefore extravascular as well as extracellular. In order to cause such a gross alteration in the partition of fluid loss after thyroxine, its extent must be considerable. Rough estimates from the above data suggest at least 100 to 200 g. of protein in a concentration of 5 to 10% or more.

Discussion

The data described above suggest the existence in the tissue spaces in myxœdema of a rich deposit of protein which is readily dispersed by thyroxine. In discussing the significance of this abnormality it will be desirable first to consider the normal environment of the cell. The work of Stirling (29) has shown that the fluid with which the cells of the body are surrounded consists of a freely circulating relatively protein-free ultrafiltrate of the blood plasma the secretion of which is regulated by the hydrodynamic pressure within the capillaries opposed by the colloidal osmotic pressure of the plasma proteins. In accepting the broad theory of Stirling it is important not to assume that the immediate environment of the cell is entirely devoid of protein. Protein appears in this medium in at least two forms. In the first place there is a small amount (about 1%) of protein dispersed throughout and circulating with the interstitial filtrates (9). Secondly, there is what is known to the histologist as the ground substance. The latter is a mucinous protein which appears to act as a scaffolding or cement which maintains architectural order amongst the cell units of the tissues and to answer this purpose it must necessarily exist in some form of fixed colloidal gel. The immediate environment of the cell therefore consists of two contrasting elements, the one fixed and colloidal, the other saline and circulating. The physical relationship of these two elements to one another is at present obscure.

Myxœdema consists of an introduction of extra protein into this environment and from the fixed appearances of the swellings it seems probable that the condition is one of expansion of the ground substance into the circulating filtrates of the blood. There is evidence, however, that the hydrodynamic balance across the capillary wall is upset by the presence of this protein. It has been shown by others and confirmed by the writer (see above) that the total volume of the plasma is diminished (30) and its percentage protein content increased (6) in untreated myxœdema.

* Plasma proteins were estimated gravimetrically (26) and total plasma volume by the vital red method (27).

Both of these changes suggest the presence in the extravascular fluids of a colloid which tends to abstract saline but not protein from the plasma. The myxœdema protein therefore contributes something to the colloidal osmotic pressure of the interstitial fluids.

The degree of disorganisation of filtration across the capillary membrane, however, is small in comparison with the high concentration (5 to 10%*) of the myxœdema protein. This discrepancy suggests that the colloidal osmotic pressure of the latter is considerably less than that exerted by the plasma proteins, or, in other words, that its molecular aggregate is considerably larger. A complex colloid such as a mucoprotein derived from the ground substance would answer to this description. Consequently the present results are entirely in harmony with Ord's original claim that myxœdema is a mucinous infiltration of the tissues, and the negative results of Halliburton and others can be dismissed as due to one or other of the causes suggested by that writer.

Concerning the source of the myxœdema protein Horsley (18) showed that after thyroidectomy in animals the cells of the parotid, normally a wholly serous salivary gland, begin to secrete a mucous fluid. Apparently myxœdema is only a more widespread manifestation of the same process.

Finally, what is the meaning of this metabolic aberration? The chemical points of resemblance between mucoprotein and chitin and cellulose suggest that one of the main functions of the former is architectural (20). Furthermore it is known that foetal tissues contain more mucin than those of the adult (15), and Wells (31) has pointed out that in this respect myxœdema resembles a reversion to the foetal state. Reviewing these clues in the light of the available evidence it seems probable that the pathogenesis of myxœdema is as follows.—In the early embryo the cells of the body are embedded in a protective matrix of mucinous jelly. As the tissues begin to differentiate and the circulation begins to develop, the bulk of this matrix becomes absorbed to make room for the clefts which transmit the saline filtrates of the blood, and in the adult only a skeleton of mucin remains. This transformation, like other phases of growth, is influenced by the thyroid gland, which continues after growth has been accomplished to hold the secretion of mucin within proper bounds. When this influence becomes impaired the balance becomes upset and an excess of mucin is formed by the tissue cells. As this accumulates the separate identity of the fixed and circulating elements which compose the normal environment of the cells becomes more or less submerged in the gelatinous swellings of myxœdema. When the abnormal protein is dispersed by thyroxine the normal hydrodynamic balance between plasma and tissue fluid becomes restored and the now watery œdema is spontaneously corrected. In this connection

* This is probably a conservative estimate as the nitrogen content of mucoprotein is low (20) and the customary factor 6.25 used in estimating protein from nitrogen loss is not strictly applicable.

it is interesting to recall the clinical observation of Byrom Bramwell (3) that transient pitting oedema of the legs often appears in myxoedematous patients who have begun to respond to thyroid treatment

Whether the smaller loss of extracellular fluid observed in the normal subject after thyroxine is referable to destruction of normal ground substance, or to dislocation of other mechanisms—such as those concerned with heat regulation—is a question which cannot be answered from such rough data as are presented in this paper

The above interpretation of myxoedema as something more than the simple quantitative expression of retarded metabolism suggested by Boothby and Harrington has recently acquired additional support from Dodds and Robertson (5), who have shown that the drug dinitro-o-cresol, while restoring the basal metabolism to normal in myxoedema, entirely fails to disperse the characteristic swellings of the disease

SUMMARY

In the normal subject the loss of body protein caused by thyroxine is accompanied by a loss of body water which contains more potassium than sodium and is therefore derived largely from the intracellular fluid compartment. This is consistent with the fact that the normal protein stores are essentially intracellular

In myxoedema a similar loss of protein and body fluid follows an injection of thyroxine, but the lost fluid contains a large excess of sodium over potassium, and is therefore contributed mainly by the extracellular compartment. Accepting protein loss and fluid loss as cause and effect, it is inferred from this difference in response to thyroxine that there is in myxoedema an abnormal extracellular accumulation of protein towards which the katabolic effect of thyroxine is specifically diverted from the normal intracellular protein stores

This protein is extravascular as well as extracellular. It appears to have a large molecular aggregate but it exerts sufficient colloidal osmotic pressure to oppose that of the plasma proteins and so to lead to a transfer of saline from the plasma to the interstitial fluids. In this way it accounts for the peculiar clinical characters of myxoedematous swellings and for the low total volume and high protein content of the plasma in this disease. Thyroxine, by destroying the abnormal protein, restores the normal hydrodynamic balance across the capillary membrane, and so promotes the elimination of the oedema fluid

These conclusions are in harmony with Ord's original definition of myxoedema as an accumulation of mucoprotein in the tissues and against the more recent view that the disease is simply a quantitative expression of lowered basal metabolism

Myxœdema may be regarded as an attempt on the part of the tissues to restore their embryonic myxomatous environment by flooding the interstitial spaces with mucoprotein

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OBSERVATIONS ON THE EFFECT OF FOOD, GASTRIC DISTENSION, EXTERNAL TEMPERATURE, AND REPEATED EXERCISE ON ANGINA OF EFFORT, WITH A NOTE ON ANGINA SINE DOLORE *

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In a previous communication, Wayne and Laplace (18) described a method for the objective study of angina of effort. It was shown that in certain patients, examined under standard conditions, the amount of exercise required in successive tests to produce pain is remarkably constant. This finding was used to study the relation of pain to pulse rate and blood pressure and to the administration of certain drugs. The observations now reported have been made in the same way to study the relationship of pain to other factors, namely, the taking of food, gastric distension, external temperature, and repeated exercise. It is to be emphasised that it is only by isolating each factor and ascertaining its effect by actual tests that apparent vagaries in the onset of attacks become explicable. As before, we have restricted our main observations to cases of angina of effort in the strictest sense, that is to say, to those cases in which exercise, and exercise alone, gives rise to pain.

The effect of meals on angina of effort

Patients with angina of effort often say that pain comes more easily when they take exercise soon after a meal. In Heberden's (5) original account of the disorder, this relationship was noted and the unknown man who wrote the historic letter to him (6) stated that he first experienced pain on walking after dinner.

We have tested six cases from this point of view. Each patient came to the hospital near midday, having eaten nothing but a light breakfast at

* Work undertaken on behalf of the Medical Research Council

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8 a m or earlier. After a half-hour's rest, the amount of exercise required to produce pain was determined. He then ate a heavy lunch consisting of meat, two vegetables, and pudding, water was allowed as a drink. A test was carried out ten minutes after the meal and in four cases a further test was made after another quarter of an hour's rest. Exercise tolerance* was definitely reduced after the meal in every case, and in most cases by about a quarter, as seen in Table I. In none of the six cases was the resting blood pressure significantly altered by the heavy meal but in all the resting pulse rate was raised by 10 to 20 beats a minute. The changes in blood pressure and pulse rate after exercise were similar in the control tests and in the tests made after a meal but after the meal the pulse rate usually fell more slowly to the resting level. This was especially noticeable in the only two cases (8 and 12) in which the duration of the pain was significantly increased after food. Fig. 1 shows the relationship of pain to blood pressure and pulse

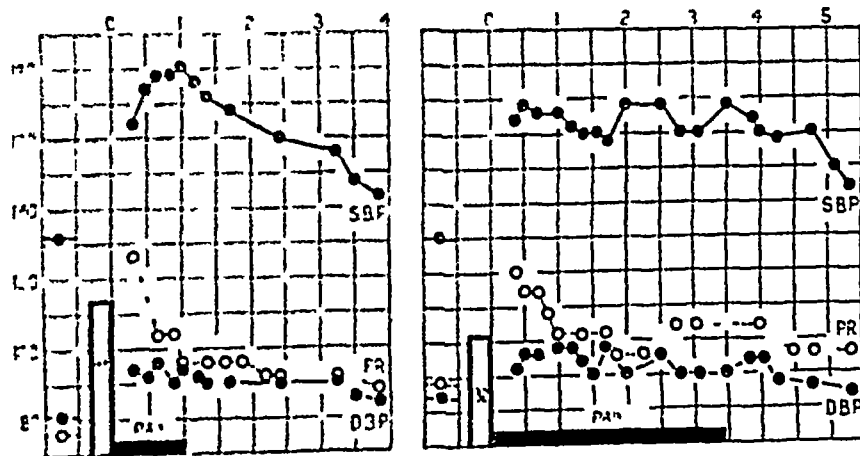


Fig. 1. Case 8. The left chart shows a control test; the right records the result of a test made half an hour after the midpoint of a heavy meal.

SBP = systolic blood pressure in mm. of mercury
DBP = diastolic blood pressure in mm. of mercury
PR = pulse rate in beats per minute

On the left of the vertical rectangle are the resting readings before exercise was begun, to the right are the readings after the patient had sat down. The number included in the vertical rectangle and its height represent the number of efforts. The length of the black horizontal rectangle gives the duration of pain.

rate in Case 8 before and after the meal. To determine whether the diminished exercise tolerance was due to simple distension of the stomach by food or to some other change such as increased blood flow to the digestive organs, we investigated the effect of inflating the stomach with air.

* Exercise tolerance refers to the amount of exercise which produces pain; it is measured by the "number of efforts," that is the number of times the patient walks over two steps of standard height. Further details of the method and of cases bearing the numbers 1 to 11 are given in the previous paper (18). Details of other cases are appended to this paper.

The effect of gastric inflation on angina of effort

The effect of gastric inflation was studied in each of the six patients whose exercise tolerance was known to be reduced by a heavy meal. After control tests of exercise tolerance had been made, a Rehfuss tube such as is used in the fractional test meal was swallowed. When the pulse rates and blood pressures had returned to resting levels, air displaced by water was slowly passed into the stomach. After amounts differing in different patients, an unpleasant feeling of fulness in the epigastrium was produced, passing off quickly when the flow of air was temporarily stopped. As the air introduced was increased to a volume varying from one to three litres in different cases, all the patients complained of epigastric pain persisting for several minutes. Some of the air was lost by eructation but X-ray examination always showed an increase in the amount in the stomach and in two cases the left dome of the diaphragm was raised and the heart displaced. During filling with air there was in every case a rise in systolic blood pressure of from 10 to 20 mm Hg, and in diastolic pressure of from 5 to 10 mm Hg. The rise of pulse rate, which occurred in every case, varied from 10 to 25 beats a minute. A few minutes after all the air had been introduced and sometimes before discomfort had passed off, blood pressure and pulse rate returned to resting levels, although percussion showed that there was still

TABLE I.

The effect of food and of gastric inflation on pulse rate and exercise tolerance in angina of effort

Case No	History of diminished exercise tolerance after food	Resting P.R.		Average number of efforts		History of diminished exercise tolerance from flatulence	Resting P.R. when tested		Average number of efforts	
		Before a meal	After a meal	Before a meal	After a meal		Before gastric inflation	After gastric inflation	Before gastric inflation	After gastric inflation
2	Yes	64	76	14	9	No	64	64	15	13
7	Yes	96	110	107	98	Yes	108	112	78	106
8	Yes	76	86	41	31	Yes	76	72	37	38
10	Yes	84	96	83	65	Doubtful	96	96	100	106
11	Yes	88	100	71	51	No	88	90	63	68
12	Yes	104	124	53	34	Yes	72	74	44	38

of cardiac enlargement and a moderate degree of dilatation of the aorta. A systolic murmur was heard at the aortic cartilage, the second aortic sound was accentuated and metallic in quality. The systolic and diastolic blood pressures after a long rest were 170 and 70 mm Hg respectively, the pulse rate was 72 beats a minute. The Wassermann reaction was positive, and the electrocardiogram normal.

Course Just before admission to hospital, his exercise tolerance was tested in the usual way. After 34 efforts at a rate of 11 a minute, he had a severe attack of pain. He was very flushed and sweated profusely, the respiratory rate had risen from 17 a minute at rest to 21. The pulse rate was raised to 140 and the systolic and diastolic blood pressures to 208 and 120 mm Hg, respectively. The pulse rate fell a little in the first minute after exercise was stopped but then remained for 11 minutes in the region of 100 beats a minute, when it started to fall. At this time the pain became less severe, but it did not disappear until 23 minutes after the end of exercise. Such severe attacks have not occurred after exercise in any of our cases of pure angina of effort, but they are common in patients who also have "spontaneous" attacks.

During the patient's stay in hospital and while in bed he suffered many attacks of angina, the pain was readily relieved by nitrites. They commonly happened after meals but sometimes occurred when he woke up at night. In one attack in which the pain was severe, the blood pressures, which were 174 mm Hg systolic and 80 mm Hg diastolic after his meal and before the pain started, rose to 200 mm and 100 mm at the height of the attack, while the pulse rate was raised from 86 to 106 beats a minute. The face was not definitely flushed but sweating was profuse. After 5 minutes, amyl nitrite was given and the pain passed away rapidly.

The effect of distending the stomach with air was tested in this patient. Some time after a meal and with no pain present a Rehfuß tube was passed. X-ray examination showed an air bubble of moderate size in the stomach. After 1,100 c.c. of air had been introduced into his stomach, he complained not only of a feeling of epigastric discomfort, but also of retrosternal pain which he recognised as that of his anginal attacks. The pulse rate had then risen from 100 to 120. X-ray examination now revealed a large gas bubble underneath, but not lifting the diaphragm or displacing the heart. The retrosternal pain, becoming more severe, was relieved in three minutes by 1/50 grain (13 mg) nitroglycerine given by mouth, the epigastric discomfort remained for half an hour.

After discharge from hospital, this patient had further severe attacks of angina relieved by nitrites and died suddenly in bed on January the 30th, 1933. A post mortem examination was not obtained.

Comment This case is reported in full, though it is the only one of those we studied in which gastric inflation produced anginal pain. It contrasts strongly with our cases of angina of effort, and resembles in many respects the cases described by Lewis (10). In these attacks of pain which

do not seem to be related to any single causative factor, are associated with a raised pulse rate and blood pressure. Lewis suggests that the coronary vessels are involved in a general vasomotor change, and that they fail to carry the extra stream of blood which the heart requires. This vasomotor change can be precipitated in a number of ways. In one of his cases pain arose regularly after food had been taken, and coming almost immediately after small amounts of food, can hardly be attributed to the increased blood requirements of the digestive organs. In both this and in the case we have just described the attacks are probably due to a vasomotor change excited reflexly by gastric distension.

The effect of flatulence on the heart

Our experiments on gastric distension have a further significance. Flatulence has long been thought to affect the heart adversely, either reflexly or, as thought by many early writers, by mechanically displacing it. Thus, Brunton (8) gives a diagram showing the way in which the heart is mechanically displaced by gas in the stomach and says "If the stomach is distended, it seems to interfere with the heart's action and may produce distress or even death." Frequent reference is made in German writings to the "gastro-cardiac symptom complex" described in 1912 by Roemheld (15, 16) who considers that palpitation, extra-systoles and precordial pain can be produced by mechanical displacement of the heart. This view is surprising when the natural mobility of the heart is considered and the extent to which it moves in such physiological processes as respiration and in turning from side to side. It is noteworthy that the heart was not mechanically displaced in the case in which we were able to induce an anginal attack by gastric inflation. Lurie and Stern (12) have recently described a "cardiodiaphragmatic syndrome" which represents the view that flatulent distension may disturb the heart reflexly. Excessive accumulation of air in the stomach is regarded as the cause of many symptoms such as shortness of breath, palpitation and anginal pain, including angina of effort, all of which are relieved if the air is aspirated and return when it is reintroduced. These symptoms, and such physical signs as systolic murmurs and changes in intensity of the heart sounds, are said to be produced even in normal individuals if the stomach is inflated sufficiently to raise the dome of the diaphragm. Verdon (17) goes so far as to attribute all attacks of angina pectoris to distension of the upper part of the alimentary canal and states that they are unconnected with the heart and are always relieved by eructation or mechanical removal of air from the stomach.

These views, in so far as they relate to angina of effort, are not supported by the experiments we have described here. For exercise tolerance was unaffected by introducing into the stomach a quantity of air, which was great enough in two cases to raise the diaphragm and displace the heart, and which in all cases appeared larger on X-ray examination than the

quantity seen except in extreme cases of air swallowing. Moreover, the pain passed away at a time when the stomach was still distended with air.

We also introduced large quantities of air into the stomachs of five normal young adults, they were able voluntarily to restrain eructation to a much greater extent than patients, so that a very large air bubble was produced, three subjects retained two litres, and two retained one litre of air. In three, X-ray examination showed that the heart had been displaced. A significant change in blood pressure, whilst air was being admitted to the stomach was noted in one subject only, the systolic blood pressure rising by 14 mm Hg. In three subjects, the pulse rate fell as soon as each fresh quantity of air was introduced into the stomach and while it was dilating rapidly. In two of these, this fall of rate was from 8 to 13 beats a minute and in the other subject 16 to 20 beats a minute. This fall in rate was constant in repeated observations. In the other two subjects, no fall in rate was noticed but a rise of 8 to 20 beats a minute occurred when epigastric pain appeared, towards the end of the observation. After large amounts of air had been passed into the stomach and were retained, discomfort, pain and the desire to eructate gradually passed off. No change from resting values in either pulse rate or blood pressure was then detected in any of the five subjects. No abnormalities of rhythm and no alteration in the heart sounds were detected. In one case, exercise to the same extent was taken before and after filling the stomach with two litres of air, and no difference in the initial or final blood pressure and pulse rates was observed.

Our results show, therefore, that while the stomach wall is being stretched as a result of a rapid increase of intra-gastric pressure, the heart may be slowed reflexly in some cases. Owen (14) reports similar results in dogs. When, however, the stomach wall has adapted itself to its new conditions we can find no evidence of any effect on the heart except displacement either in normal individuals or in patients with angina of effort.

It is noteworthy that four of the patients with angina of effort said that attacks came after less exercise "when they had wind" although we found by experiment that gastric inflation had no effect. Careful questioning, however, elicited that flatulence was always much more pronounced soon after a meal and it is to the effect of food that we attribute any difference in exercise tolerance which they had detected. This and other similar factors should be excluded before any cardiac symptom is attributed to flatulence. Our evidence suggests, however, that a paroxysm may be determined by flatulence in cases of angina with "spontaneous attacks". It must be remembered in this connection that anginal pain may be wrongly interpreted as gastric by the sufferer with consequent air swallowing and eructation, flatulence may, therefore, be associated with, although not the cause of, an attack.

The effect of variations in external temperature on angina of effort

It is generally believed that cases of angina are more liable to attacks in cold weather and most of the cases we have interrogated have thought that pain arose after less exercise in winter than in summer. We now have records of exercise tolerance of many patients over one or two years taken at approximately monthly intervals and these show no obvious seasonal variation. Most patients, however, have too wide a variation in exercise tolerance on successive visits to make this evidence conclusive and we, therefore, tested the matter directly. Six cases were chosen, of which five thought they were worse in cold weather. The patients sat without jacket or waistcoat in the open air at temperatures ranging from 6.5° to 13.0°C until they said they felt cold, all but one (Case 7) developed cold hands and shivered. The exercise tolerance was then tested and usually the test was repeated after a further rest in the open air. The patients were then given a prolonged rest in a room at a temperature between 23° and 28°C and when

they were thoroughly warm, the test was again carried out, usually in duplicate. The results summarised in Table II show no clear difference in exercise tolerance at the low and high temperatures, the first observation on Case 7 and the second on Case 10 gave border-line results, the former suggesting a possible slight improvement in the cold, and the latter in the warm atmosphere. In the warm atmosphere, the resting pulse rate was usually higher, and the systolic blood pressure always definitely lower, often the diastolic blood pressure was slightly lower. After exercise sufficient to bring about an attack, the blood pressures were often lower in the warm atmosphere but no significant change in the pulse rate was detected except in Case 8 where the pulse rate after exercise was 6 beats a minute greater in the warm room.

The lower temperatures chosen were normal for this country in winter but the effects on the patients were intensified by depriving them of some of their clothing and it is unlikely that, in their daily life, they would for long tolerate cold sufficiently severe to cause them to shiver. The upper temperatures are higher than are met with in England either indoors or out except on occasional days in summer.

The effect on pulse rate, blood pressure and cardiac output of varying external temperatures over a wide range has been studied by Grollman (4). In his normal subjects, the pulse rates and the blood pressures at 25°C differed from those at 5°C by amounts comparable to those which we have noted in our cases of angina. Grollman found, however, no change in cardiac output at temperatures between 0°C and 28°C. At the lower temperatures the output is not raised by the small amount of work represented by the increased tone of the muscles and by shivering, and at higher temperature it is not affected by the increased blood flow through the skin until the external temperature rises above 28°C. It did not surprise us, therefore, to find no difference in exercise tolerance at different temperatures, the energy expenditure of the heart is not greatly affected, for the output is the same, and any difference due to the small rise in pulse rate at higher temperatures is offset, in part at least, by a greater fall in mean blood pressure. Our results also suggest that external temperature is without appreciable effect on the degree of dilatation of the coronary vessels in angina of effort. It remains to explain the common belief that temperature is an important factor in bringing about attacks of angina pectoris. In cases of the type described by Lewis (10), it is reasonable to suppose that sudden changes in the temperature of the patient's environment may initiate a vasomotor change in which the coronaries become involved. But in our present series of cases of pure effort angina we should have been misled had we not checked patients' statements by direct tests. One of our patients gave us the probable explanation of the discrepancy when we told him that we had not confirmed his belief. He pointed out that we had made him exercise at the same rate in all the tests, whereas had he been free as in his daily life to choose he would have walked more quickly in the cold, and more slowly in the hot atmosphere,

alterations in the rate of exercise had a definite effect on exercise tolerance in this case and in others as we shall show later. Other patients when questioned agreed with this view. It is to be remembered too that patients are apt to be handicapped by heavy clothing and head winds in winter.

The effect of repeated exercise in angina of effort

Some patients say that having rested after a first attack, a second attack is less easily provoked. Two such patients were tested. They were warned to come very slowly to hospital and were made to rest a long time before the

TABLE III
The effect of varying periods of rest on exercise tolerance

Case	Time	Interval between tests	B P at start		P R at start	1 florta	1 florta per min	B P at end		P R at end
			Syst	Diast				Syst	Diast	
C	7a	Initial	178	98	72	58	10.1	201	110	114
	b	1 Min	212	110	108	20	10.3	212	120	114
	c	5 Min	174	100	80	81	10.2	194	112	120
	d	15 Min	174	104	80	116	10.0	190	112	120
	e	75 Min	156	98	72	60	10.0	194	110	114
Ca	10a	Initial	126	84	80	48	10.1	166	100	114
	b	2 Min	150	88	90	34	10.1	160	90	114
	c	12 Min	126	90	78	60	9.9	154	86	114
	d	15 Min	128	88	76	64	9.9	154	84	108
	e	70 Min	120	90	76	60	9.9	160	92	108
	f	65 Min	120	88	76	50	9.9	150	92	114
Cb	1a	Initial	120	72	76	16	10.6	150	60	102
	b	1 Min	140	70	76	10	10.5	160	68	102
	c	4 Min	120	68	72	12	10.5	146	70	102
	d	7 Min	126	68	72	14	10.5	150	60	104
	e	15 Min	126	72	76	16	10.6	156	60	104
Cc	2a	Initial	140	88	76	13	10.4	160	90	114
	b	4 Min	140	88	72	7	10.5	154	90	120
	c	15 Min	146	88	72	10	10.0	154	94	114
	d	75 Min	144	88	64	15	10.0	154	90	114

The above protocols are representative and were repeated at least once on each patient with similar results.

tests were begun. The results fully confirmed their statements except when the period of rest was very short. Representative protocols (Cases 7 and 10) are given in Table III. It will be seen that the number of efforts required to produce pain was diminished when exercise was taken within two minutes after the previous test, but if a longer rest was allowed exercise tolerance was increased. After about an hour's rest, however, exercise tolerance was the same as in the initial test. Two other cases which were fully examined also gave clear evidence of a phase of increased exercise tolerance preceded by one of decreased tolerance. On the other hand two further patients (Cases 1 and 2, Table III) showed no phase of increased tolerance, a second test made within 30 minutes of the initial one showed that exercise tolerance was reduced, the reduction being greater the shorter the interval. After 30 minutes, exercise tolerance remained constant. We have represented schematically the results from the two types of case in Fig 2. Tests on

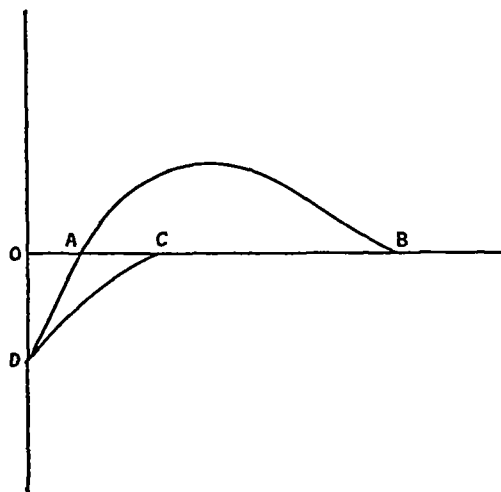


Fig 2 The effect of varying periods of rest on the exercise tolerance of two different types of case is shown schematically. Exercise tolerance is represented vertically and the periods of rest between the end of one attack and the start of the next test is represented horizontally. The curve D A B represents the type of case showing a phase of increased tolerance and the curve D C the type with no phase of increased tolerance.

other cases suggest that in angina of effort there is usually a phase of increased exercise tolerance, but, as this is often short, it is difficult to demonstrate clearly. In most cases, exercise tolerance is unaltered when fifteen minutes rest is given.

Discussion Wayne and Laplace (18) concluded that pain is produced in angina of effort when the heart increases its energy expenditure without a concomitant increase in the coronary blood flow, pain disappears as the energy expenditure of the heart diminishes when the patient rests.

During the phase of increased exercise tolerance after an anginal attack (A B in Fig. 2) there was no significant difference in the blood pressure and pulse rate recorded at the start and the end of exercise when compared with the tests done after a very long rest (Table III, Case 7 tests *c* and *d*, Case 10 tests *c*, *d*, and *e*). This phase, therefore, cannot be explained as one in which there is a diminished energy expenditure of the heart in response to exercise and we suggest that the increased tolerance is due to dilatation of the coronary vessels as a result of the events of the previous attack. Nitroglycerine increased exercise tolerance considerably in all the cases showing this phase of increased tolerance and a previous attack of angina would thus appear to act similarly to nitroglycerine although in each case a greater effect is produced by the drug. During the short phase (D A in Fig. 2) in which a diminished tolerance is exhibited blood pressure and pulse rate are both much raised when exercise begins and this presumably more than outweighs any effects from increased coronary flow (Table III, Cases 7, test *b* and 10, test *b*).

In the two cases of ours which showed no phase of raised exercise tolerance we suggest that the coronary circulation though more than adequate for the needs of the heart at rest remained unaltered during exercise for the exercise tolerance of one was unaffected and of the other only slightly increased by nitroglycerine in full doses. It has been shown in the case of the limb by Lewis, Pickering and Rothschild (11) that the time taken for the recovery of the process in the muscle fibre which gives rise to pain is much longer than the time taken for pain to pass off. Similarly in these two cases exercise taken soon after the disappearance of pain even though pulse rate and blood pressure have returned to resting levels, finds unrecovered muscle fibres in the heart and pain returns quickly.

The effect of varying the rate of exercise

In all the tests we have described so far, patients were allowed to choose their rate of walking over the steps but this rate once chosen was adhered to in subsequent tests. In six cases, after the control tests had been established in the usual way, further tests were made at approximately half the standard rate. In four cases a definite increase was noted in the number of efforts performed. In the two others, no significant alteration was found in repeated tests, and it is noteworthy that these were the cases in which we had been unable to detect any signs of dilatation of the coronary vessels during exercise, and little or none after nitroglycerine (Cases 1 and 2 Table III). Typical protocols are given in Table IV from one of these cases and from one of the other cases to show the usual extent of the increase in exercise tolerance at the slower rate. Finally, in two of the cases showing increased tolerance at rates of exercise below the standard, a reduction in tolerance was found when the rate was increased above the standard.

To understand these results it must be clearly realised that even where reducing the rate did not affect exercise tolerance, the actual time taken from the start of exercise to the onset of pain was much increased (Table IV) When exercise begins, the rate, output and energy expenditure of the heart immediately rise above their resting level. The energy expenditure does not rise so quickly, however, at slow rates as at rapid rates of exercise, so that a longer time elapses before it becomes too great for the coronary flow. In the cases in which the coronary vessels are incapable of dilatation

TABLE IV
The effect of exercise at different rates

	Test	BP at start		PR at start	Efforts	Efforts per min	Time taken over exercise sec	BP at end		PR at end
		Syst	Diast					Syst	Diast	
iso 1	1st Control	130	70	72	16	10.0	96	150	74	108
	2nd Control	132	72	68	16	10.0	96	146	70	108
	Exercise at slower rate	124	76	72	18	6.9	153	160	70	108
	Exercise at slower rate	128	72	72	18	5.0	216	140	72	102
iso 13	1st Control	110	70	72	36	14.0	155	156	80	102
	2nd Control	116	72	62	36	13.5	160	152	88	96
	Exercise at slower rate	124	74	64	42	7.0	360	150	80	96
	Exercise at slower rate	120	76	60	45	6.6	410	156	88	102
	Walking on flat at 2 miles an hour	120	70	64	900 yds	58 yds	940	124	70	93

on exercise, the lowered energy expenditure at half the standard rate can be carried for about twice the time, and hence exercise tolerance is unaffected. In the other cases it may be supposed that the coronary vessels dilate early in exercise, and the diminished load on the heart at half the standard rate can be borne for more than twice the time so that exercise tolerance increases.

Patients do not usually distinguish clearly between the time taken over exercise and the distance walked, they all say quite correctly that at slower rates of exercise, the pain takes much longer to come but they do not usually realise that they have not performed a correspondingly greater amount of exercise.

Angina sine dolore

While searching for cases of angina of effort suitable for investigation, we encountered a patient with the following history. H. H., an intelligent single man aged 59 years, employed as a clerk, came to hospital on the 22nd of March, 1933. He complained of attacks of an uncomfortable sensation in the lower part of the chest. There was no past history of rheumatic fever, chorea or venereal disease, the Wassermann test was negative. For about a year he had noticed that he became unusually breathless on taking exercise.

The attacks which had started two months previously as he was walking to work were brought on only by exercise. After walking for about 20 to 60 yards on the level, he had a sensation of pressure in the chest, which he insisted was not in the least painful, sometimes he felt as if his breathing had stopped. At first the attacks frightened him, giving rise to dread that he was going to die. In many attacks, but not in all, he felt giddy and faint

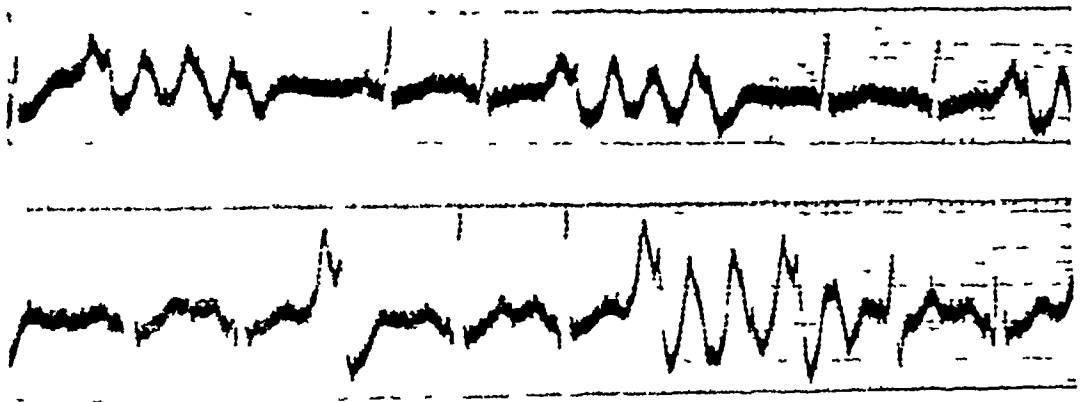


Fig. 3. An electrocardiogram (Leads I and III) after exercise, showing paroxysms of very rapid ventricular action verging on fibrillation.

and often lost consciousness, palpitation was sometimes experienced. The sensation in the chest and the giddiness usually passed off together after about 30 seconds rest.

Clinical and X-ray examination showed that the heart was slightly enlarged. Signs of venous congestion were absent. The pulse rate at rest was 72, and the rhythm regular except for a very occasional extrasystole, no murmurs were heard. The radial and brachial vessels were tortuous and the empty vessels could be rolled under the fingers, the retinal vessels were normal. The systolic blood pressure was 130 and the diastolic pressure 90 mm Hg. The electrocardiogram showed normal complexes and occasional ventricular extrasystoles. The other clinical and laboratory findings revealed nothing abnormal.

The patient was exercised until he began to feel giddy and faint, and to experience the uncomfortable sensation in his chest. Electrocardiograms were taken as soon as possible after symptoms were experienced. Fig 3 shows the type of curves obtained, complexes of supraventricular type alternate with paroxysms of very rapid ventricular action verging on fibrillation. These abnormal beats were wholly ineffective, the pulse often being absent at the wrist for as long as five seconds. The observation was made repeatedly.

The patient was greatly improved by rest in bed and the administration of quinine, after a week's treatment, exercise sufficient to cause considerable breathlessness no longer gave rise to paroxysms of arrhythmia or to faintness. Four somewhat similar cases of paroxysmal ventricular tachycardia related to exercise have recently been recorded by Wilson, Wishart, Macleod and Barker (19).

The central feature of the attacks described by our patient was a sensation of pressure in the chest which bore a constant relation to exercise and was accompanied by a fear of death. Such cases are usually diagnosed as "angina sine dolore". Gardner (2), who coined the term in 1877, applied it to an "indefinable and indescribable sensation not distinctly accompanied by local pain" and the sensation subsequently came to be identified with Latham's (9) "sensation of approaching dissolution". Thus Allbutt (1) and Mackenzie (13) regard such a sensation as sufficient to establish an attack as anginal even in the absence of pain, the diagnosis is strengthened if a relationship to exercise can be shown. Now, patients suffering from undoubted angina very rarely complain spontaneously of such a fear of death, when they do so, it will usually be found that the idea has been suggested to them. None of our cases of angina of effort have described such a sensation. On the other hand, the onset of an abnormal rhythm, as in our case, or even an occasional extrasystole may give rise to a sensation which the patient finds difficult to describe and which frightens him. The "universal pause in the operations of nature" which the unknown man who wrote to Heberden (6) described, though represented by later writers as an example of the sense of impending dissolution is clearly interpretable as due to extrasystolic irregularity of the heart. It is when such cardiac disturbances are associated with exercise that they most easily lead to the diagnosis of "angina sine dolore". Mackenzie (13) alone seems to have realised that some of these cases were due to the onset of an abnormal rhythm.

It has been offered as a proof of the reality of 'angina sine dolore' that sufferers may die in one of their attacks. Such an outcome would not be surprising in such a patient as the one we have described and would be attributable to a complete ventricular fibrillation.

We have been unable to find in past records a single case described as "angina sine dolore" which could not be interpreted in other ways. Few observations during attacks, observations so essential to analysis, have been

CASE RECORDS

There have been no further deaths among the 11 cases previously reported (18). Exercise tolerance and response to nitroglycerine has diminished in Case 1. Exercise tolerance has diminished in Case 2 and increased in Cases 8, 10 and 11, in the other cases it has remained unaltered.

Case 12 R T, a married man aged 60, was a clerk and later a garage hand.

History 25.11.32 In 1918 while hurrying to work he experienced a sharp pain behind the sternum which passed off when he rested. He had occasional attacks from 1919 to 1927 but being a sedentary worker was able to avoid severe exercise. From 1927 to 1930 he worked as a garage hand and had numerous severe attacks so that he ceased work in 1930. The pain is now brought on by a walk of 200 yards on the level. It still comes on exercise and on exercise alone. It is situated behind the sternum and in the 3rd and 4th left intercostal space and in severe attacks spreads down both arms to the elbows, it passes off in about 10 minutes if he rests. It is worse on exercise after a meal but no relationship to the seasons has been noticed. He also complains of attacks of momentary loss of consciousness, apparently vaso-vagal fainting attacks. These are unassociated with the attacks of pain. He does not easily become breathless.

Examination He becomes more breathless than normal on exertion. There are no signs of congestive failure. The heart shows no signs of enlargement nor of a valve lesion. An occasional extrasystole is present at rest. The peripheral vessels appear normal. The Wassermann reaction is negative. The electrocardiogram shows isoelectric T waves in lead II and inverted T waves in lead III. While in hospital, he was discovered to have glycosuria and a sugar tolerance test showed him to be a mild case of diabetes mellitus. This was easily controlled by diet.

Results of tests He became more breathless than normal on exercise. The resting blood pressure was 170/86 and pulse rate 76. The average number of efforts to produce pain was 37 and the average duration of pain 2 minutes and 15 seconds. The duration of pain was reduced slightly by amyl nitrite and considerably by pressure on the carotid sinus. Both nitroglycerine 1.3 mg (1/50 grain) and erythrol tetranitrate 64 mg (1 grain) doubled exercise tolerance and reduced the duration of pain.

Case 13 W W, is a married man, aged 62, employed as a fitter's mate.

History 30.6.33 Six months ago while carrying a heavy tube at work he experienced pain behind the lower end of the sternum which passed off when he stood still. He has since had many such attacks, always on taking exercise and never at rest. At first he could walk about half a mile on the flat before pain came but now a brisk walk of a hundred yards will start an attack. The pain which lasts for a few minutes is dull and in severe attacks spreads down both arms as far as the wrists. Associated with it is a throbbing in the chest but he thinks this is a separate sensation. No difference has been noticed in exercise tolerance in hot and cold weather or after a meal. He has become breathless on exertion for about a year.

Examination He becomes more than normally breathless on exertion. There are no signs of congestive failure. The heart shows neither clinical nor X-ray evidence of enlargement. There are no signs of valve lesion. The peripheral vessels are normal. The Wassermann reaction is negative. The electrocardiogram shows inverted T waves in leads II and III.

Results of tests The average resting blood pressure was 120/72 and the pulse rate 72. The average number of efforts to produce pain was 17 on admission to hospital and the average duration of pain was 1 minute. Nitroglycerine 1.3 mg (1/50 grain) more than doubled exercise tolerance without affecting the duration of pain but the pain now had no throb associated with it. After this observation the patient was certain that the throbbing was not an essential quality of the pain. Amyl nitrite reduced slightly the duration of pain. Exercise tolerance rose to an average of 36 efforts after rest in bed in hospital for 5 weeks and it has remained at this level for 6 months.

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OBSERVATIONS ON ANGINA PECTORIS AND INTERMITTENT CLAUDICATION IN ANÆMIA *

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AN analogy has frequently been drawn between angina pectoris and intermittent claudication, and in recent years much evidence has accumulated to show that the two kinds of pain are due to similar mechanisms operating in the muscles of the heart and limbs (Lewis, Pickering and Rothschild (18), Wayne and Laplace (28)). Believing in this view and recognising that in severe anæmia angina pectoris is not infrequent, it seemed curious to us that in the same types of anæmia intermittent claudication had not been described. Our investigation began when a grossly anæmic patient, presenting no signs of peripheral vascular disease, told us that if he walked a short distance he was brought to a halt by severe pain in the legs, which disappeared after a brief rest. We then closely enquired both for this symptom and for anginal pain in 25 patients admitted consecutively to hospital with hæmoglobin concentrations of 50% or less, and who had been walking about before admission. The results are summarised in Table I. We found that 7 had experienced an aching pain in the muscles of the limbs, induced by exercise only and quickly relieved by rest, after cure of the anæmia the pain was no longer experienced in 6 of them, while in one it was but slight. No sign of structural disease of the limb vessels was found in any of these 7 patients. In all of them we were able to elicit pain by resisting movements of the legs while the patients were lying down, and to show that the pain so elicited had the same characteristics as the pain of intermittent claudication. The observations on four of these patients are described later (page 307).

Intermittent claudication has probably escaped recognition in severe anæmia because it is usually a minor complaint, and one that is liable to be grouped amongst the paræsthesiæ that are common in the pernicious form.

Since Herrick and Nuzum (11) in 1918 drew attention to the occurrence of angina pectoris in anæmia, many cases have been reported, but there is

* Work undertaken on behalf of the Medical Research Council

disagreement as to its frequency. Thus in pernicious anæmia, angina pectoris was found by Coombs (5) to occur in 8 of 36 cases, whereas Willius and Giffin (30) noted it in only 43 of 1,560 and Wilkinson (29) in only 3 of 270 cases. This disagreement is probably due in part to a difference in method, for Coombs saw all his patients, whereas Willius and Giffin only analysed case records. Unless specific enquiry is made, the pain, which is often a minor complaint, readily escapes notice. It is also partly due to a difference of opinion as to what may be accepted as angina pectoris, for Wilkinson remarks that a number of his patients had "pseudo-angina". Several other observers have reported isolated cases (Cabot (3), Connor (4), Giffin (9), Levine (15), Reichel (21), Witts (31), Gwyn (10), Elliot (8)), but we can find only six cases in which reference is made to improvement or disappearance of pain with cure of the anæmia, and in these the evidence is incomplete.

In our series of 25 patients 8 complained of pain over the sternum with or without radiation to the arms, the pain could be induced only by exercise and was relieved by rest, in 6 this pain was no longer experienced after the anæmia had been cured, in 2 it persisted. Two other patients (Cases 6 and 8) complained of tightness over the sternum which was induced only by exercise and relieved by rest, in one, this was associated with numbness of the left upper arm, in both, the symptom disappeared after the anæmia was cured. Accepting the view that tightness over the sternum has the same origin as anginal pain on effort, we have thus 8 typical cases and two atypical cases in the 25 anæmic patients, an incidence which is of the same order as that found in pernicious anæmia by Coombs (5). We do not wish to stress the precise figures we have obtained for the incidence of either intermittent claudication or angina pectoris in our series of anæmic patients, since it is small, but to point out that these complaints are neither uncommon nor restricted to any one form of anæmia.

In order to obtain more information about the nature and mechanism of these pains, both have been studied under controlled conditions.

Intermittent claudication

We have said that 7 of our 25 anæmic patients complained of pain in the legs induced by walking and relieved by rest. Four of these patients, and 5 others who had not experienced pain in the legs on walking, were chosen to exercise their limbs under standard conditions in the anæmic and non-anæmic states. In none of these patients were there any signs of involvement of the nervous system or of peripheral vascular disease, in all, the main vessels pulsated freely at wrist and ankle and the reactive hyperæmia test was normal. Exercise consisted of maximal flexion of the index finger or maximal extension of the ankle joint at the rate of one movement per second as described by Lewis, Pickering and Rothschild (18), the tension developed by each patient was the same before and after cure of the anæmia. The results of the exercise tests, summarised in Table II, are briefly as follows.

TABLE II—continued

Patient Division B	Hb %	Limb	With circulation free Pain			With circulation arrested Pain		
			Begins	Intolerable	Goes	Begins	Intolerable	Goes
			min sec	min sec	min sec	min sec	min sec	min sec
W H (5)	38	Right leg	2 35	4 00	0 03	0 54	2 39	0 04
		Left leg	1 19	4 15	0 03	1 07	2 04	0 02
	80	Right leg	None in 6 min			0 48	2 43	0 04
		Left leg	None in 6 min			1 07	2 15	0 05
L L (11)	35	Right leg	1 40	3 00	0 07	1 02	1 27	0 06
		Left leg	1 37	4 07	0 05	1 07	1 42	0 07
	98	Right leg	None in 6 min			1 30	1 55	0 05
		Left leg	None in 6 min			1 28	1 50	0 03
G L (20)	37	Right leg	1 31	2 20	0 11			
		Left leg	1 18	1 57	0 10			
	90	Right leg	None in 6 min					
		Left leg	None in 6 min					
O D (23)	36	Right arm	1 24	2 33	0 12	0 29	0 54	0 05
		Left arm	1 40	2 47	0 13	0 25	0 46	0 06
	85	Right arm	None in 3 min			0 38	0 55	0 02
		Left arm	None in 3 min			0 40	0 50	0 03
Division C								
W P (26)	38.5	Right leg	3 25			1 10	2 40	0 04
		Left leg	2 35			0 55	2 15	0 05
	88	Right leg	None in 8 min			1 00	3 26	0 06
		Left leg	None in 8 min			0 55	2 28	0 06
	38.5	Right arm	1 25	2 15*		0 55	1 15	0 05
		Left arm	1 20	1 50*		0 53	1 20	0 04
	88	Right arm	2 00	3 55†		0 47	1 08	0 04
		Left arm	2 05	4 15†		0 47	1 28	0 03

* Pain severe but not intolerable † Pain slight, exercise stopped through fatigue

pain indistinguishable from that of intermittent claudication, for like the latter it is a continuous aching pain developing in the working muscles increasing steadily as exercise continues until further work may be impossible, it disappears quickly with rest, but is maintained during circulatory arrest even if exercise ceases.

In the non-anæmic (cured) state, the patients with one exception behaved essentially as normal subjects. Thus, with free circulation G experienced no pain, and 2 a slight ache which developed only after prolonged exercise and never became severe. In only one patient (Case 14) was the ache severe but it was less intense, even after twice the amount of exercise, than it had

been during the anæmic state. In all patients exercise with arrested circulation produced pain in the times usual to normal untrained subjects.

The similar behaviour of the symmetrical limbs of all the patients, and of the upper and lower limbs of Cases 1 and 26, suggests that the development of pain in the anæmic state is due to a general cause affecting all the limbs equally. As Table II shows, there was no essential difference in the behaviour of those patients who had experienced pain in the legs on walking (Division A), and those who had not (Division B), when tested under standard conditions. We can only suppose that the patients of Division B had not walked sufficiently far or quickly to induce the pain in their limbs, two of them were stopped by anginal pain and two by breathlessness, intermittent claudication thereby being conceded. Thus the development of severe muscular pain during exercise with free circulation seems to be related to only one factor, the presence of severe anaemia. Table II shows that when the limbs are exercised with arrested circulation, the time taken for pain to become intolerable is little influenced by the condition of the blood. Thus there seems to be no permanent change induced by anaemia in the tissues of the limbs or nervous system favouring the development of muscular pain. The pain developing during exercise with free circulation in anaemia must therefore be ascribed to some abnormality of the circulation to the active muscles, and the low oxygen-carrying power of the blood at once comes to mind. To exclude the other possibility, that the bloodflow to the active muscle is less during anaemia than after its cure, we have compared the bloodflow to the forearm at rest and after given amounts of exercise in three anæmic patients with that in the same patients after the anaemia had been cured. The forearm was immersed for at least 20 minutes in water at 32 to 34°C and the resting bloodflow determined by the method of Howlett and Van Zwaluwenburg (12). The effects of exercise were investigated in two ways (18, 16). In series A (Table III), the circulation to the forearm being arrested by a cuff on the upper arm, a rubber ball was squeezed maximally by the hand once per second until pain stopped further exercise. Then, after adjusting the plethysmograph, the pressure in the cuff was abruptly reduced to 60 mm Hg and the inflow curve recorded. By releasing and reimposing 60 mm Hg pressure in the cuff, inflow curves were repeated every two minutes until the bloodflow became normal. In series B the cuff was placed on the upper arm but not inflated, the ball was squeezed maximally once a second until pain was severe, the ball was then squeezed once more to empty the forearm of blood and the circulation immediately arrested by inflating the cuff. Inflow curves were then recorded as in series A.

The results summarised in Table III show that in two of these patients the bloodflow after exercise was the same, and in the third greater, in the anæmic state than in the non-anæmic state. We may conclude that exercise produces at least as great an increase in bloodflow to the muscles during the anæmic as in the normal state. The pain experienced by the anæmic

patients during exercise with free circulation is not due to a deficient blood-flow, but to an inadequate oxygen supply to the active muscles

In passing, it may be noted that the rate of bloodflow in the resting arms of these patients showed no constant differences corresponding to the condition of the blood. It seems likely, therefore, that the increased circulation rate generally accepted as occurring in anæmia (6, 19, 23) is not accompanied by an increased flow through the limbs. In this connection it may be recalled that in anæmic patients Hewlett and Van Zwaluwenburg (12) found that the bloodflow through the arm was towards the upper limit of normal, while Stewart (27) found the bloodflow through the hand to be less than normal.

TABLE III

Shows the bloodflow to the forearm in c.c. per 100 c.c. tissue per minute before and after exercise in 3 patients before and after treatment for anæmia

Case	Date	Hb %	Room temp °C	Bath temp °C	Duration (sec)		Bloodflow (c c)		Returns to normal min	
					Arrest	Exercise	Resting	After exercise		
A C (10)	A	12 9 33	38	21	34	120	37	7 5	58	20
		10 1 34	88	21	34	120	37	4 3	35	12
	B	12 9 33	38	21	34	60	65	6 9	80	20
		10 1 34	88	21	34	60	65	6 0	38	16
W H (5)	B	25 8 33	42	21	34	60	225	5 7	52	16
		19 12 33	76	21	34	60	225	7 2	51	16
W P (26)	A	16 8 33	40	21	32	140	57	2 6	26	14
		11 9 33	88	21	32	140	57	5 5	27 5	14
	B	22 8 33	47	21	33	45	150	4 2	41	—
		11 9 33	88	21	33	45	150	3 6	45	—

Angina pectoris

We have already mentioned that 8 of our anæmic patients complained of pain over the sternum induced by exercise and relieved by rest. Of these, 6 were asked to walk over the special set of steps described by Wayne and Laplace (28) until they experienced the pain, or could walk no more. In 4 the pain was reproduced, in the other 2 cases exercise was stopped by giddiness and breathlessness. In each of these 4 patients the pain showed the usual characteristics of angina of effort. Thus it came after a constant amount of exercise, it passed away in one or two minutes with rest, from beginning to end it was continuous and was never throbbing or stabbing. In the two anæmic patients complaining of tightness over the sternum, this sensation was also elicited by walking over the steps, it came after a constant amount of exercise, continued without a break, and subsided in one or two minutes with rest.

In each patient the tests were repeated at various times during treatment. In the two patients experiencing tightness, and in two of those experiencing pain during exercise in the grossly anæmic state, these sensations were no longer produced even by vigorous exercise when the hæmoglobin concentration exceeded 50%. The actual exercise tolerances, measured by the number of walks over the steps necessary to produce pain, are given in the case histories, for different hæmoglobin percentages. In two cases exercise tolerance improved gradually with rising hæmoglobin content of the blood, but anginal pain was still provoked, though by more exercise, when the hæmoglobin content was within normal limits. In Table IV the exercise

TABLE IV

Shows the gradual increase in the number of efforts necessary to produce anginal pain, corresponding to the rising hæmoglobin concentration of the blood in Case 13

Date	Hb %	Number of Efforts
29 12 33	45	5, 6
1 1 34	50	6
2 1 34	50	7
9 1 34	62	10, 10
12 1 34	62	9, 10
17 1 34	63	9, 11
27 1 34	66	13, 12
10 2 34	80	23, 25
13 2 34	85	23, 26
16 2 34	84	26, 26
19 2 34	88	33
21 2 34	88	33, 33

tolerance of Case 13 is seen to vary with the hæmoglobin concentration. Case 19 showed a similarly increased tolerance from 10 efforts at a hæmoglobin concentration of 65% to 22 efforts at a concentration of 90%. Details are given in the case history. In both cases the duration of pain was shortened by the administration of amyl nitrite. Since in both of these patients angina persisted in the non-anæmic state, they can best be explained as cases of coronary disease in which pain came more easily when anemia was also present.

Dietrich and Schwiegk (7), and Rothschild and Kissin (24) have shown that in certain patients suffering from angina pectoris, pain can be induced by breathing air deficient in oxygen, and have ascribed the pain to the direct

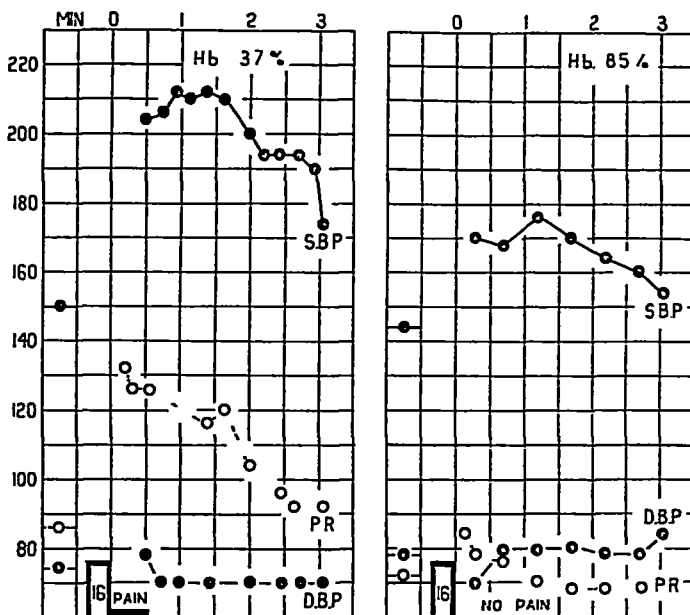


Fig 1 (Case 20) The chart on the left shows the effect of exercise sufficient to produce pain in the anæmic state, the right chart records the effect of the same amount of exercise after cure of the anæmia. There is a much greater rise in heart rate and the blood pressure is raised less in the anæmic than in the non anæmic state. In this and subsequent figures S.B.P. and D.B.P. = systolic and diastolic blood pressure in mm Hg. P.R. = pulse rate in beats per minute. The hæmoglobin content of the blood is given at the top of each chart. On the left of the vertical rectangle are the resting readings before exercise was begun, to the right are the readings after the patient had sat down. The number included in the vertical rectangle and its height represent the number of efforts. The length of the black horizontal rectangle gives the duration of pain.

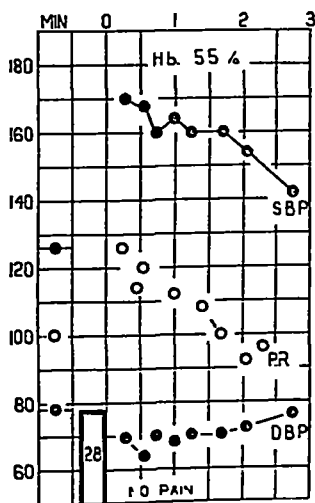


Fig 2 (Case 20) The effect of exercise after 1.3 mg (1/50 grain) of atropine sulphate had been injected intravenously when the hæmoglobin content of the blood had risen to 55%. The rise in heart rate is comparable to that associated with pain when the hæmoglobin concentration was 37% (Fig 1) yet no pain is now produced.

effect of anoxæmia on the myocardium. It is, however, uncertain how far alterations in the energy expenditure of the heart may have contributed to the production of pain, since measurements of pulse rate and blood pressure are not given. It is well recognised that profound circulatory changes may occur in anæmia, Liljestrand and Stenstrom (19) and Richards and Strauss (23) have shown that the output of the heart is increased and Dautrebande (6) found a 300% increase in cardiac output at a hæmoglobin concentration of 20%, with a return to a normal value when the hæmoglobin concentration rose above 50%. Alterations also occur in the resting heart rate and blood pressure to an extent which differs in different patients.

In all the cases studied by us, the reaction of pulse rate and blood pressure to exercise in the anæmic and non-anæmic states suggested that factors other than the effect of anoxæmia had to be taken into account in

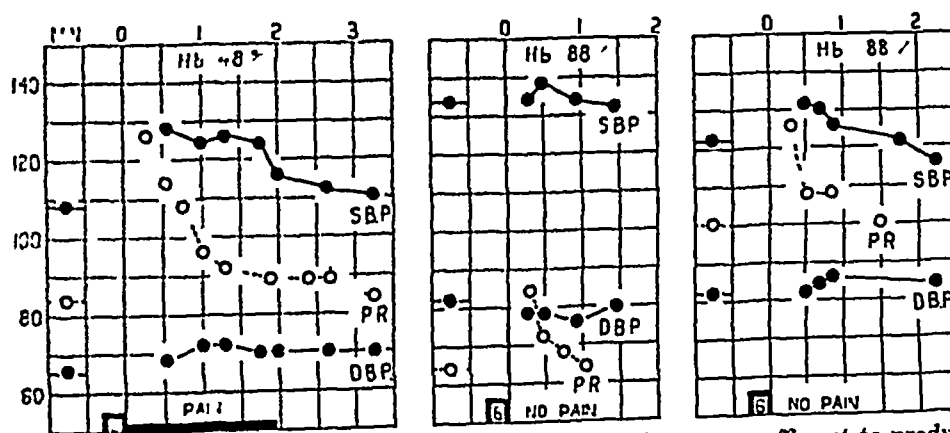


Fig 3 (Case 13) The chart on the left shows the effect of exercise sufficient to produce pain in the anæmic state, the middle chart shows the effect of a comparable amount of exercise after cure of the anæmia, the chart on the right shows the effect of exercise in the non anæmic state after the intravenous injection of 1.3 mg (1/50 grain) of atropine sulphate

attempting to explain the onset of anginal pain. It has been previously shown by Wayne and Laplace (28) that, in angina of effort, the appearance of pain is closely related to a rise in heart rate, which increases the energy expenditure of the heart. In every case we have tested, the rise in heart rate after exercise in the anæmic state was greater than after the same amount of exercise in the non-anæmic state. Figs 1, 3 and 4 all show this well. But by exercising 2 patients in the non-anæmic state after injecting atropine sulphate we were able to obtain without pain, rises in heart rate which in the anæmic state had been associated with pain. Figs 2 and 3 show such a result. It is clear therefore that the diminished oxygen supply to the myocardium is the more important factor in producing anginal pain in the anæmic state, although the exaggerated rise in heart rate probably contributes.

A further factor which must be taken into account is the change of blood pressure in anæmia. In some cases of anæmia we have found that the

general level of mean blood pressure is greatly reduced both before and after exercise. Fig 4 shows that in Case 21, after a given amount of exercise, the mean blood pressure was about 40 mm lower in the anæmic than in the non-anæmic state and Case 8 showed similar changes. These falls in mean pressure are greater than those which were shown by Wayne and Laplace (28) to be without influence on the onset of anginal pain in simple angina of effort. Anrep and King (2) have shown that the coronary flow in the heart lung preparation falls considerably with a fall in the mean blood pressure, and although compensatory factors no doubt come into play in the intact anæmic subject, a large fall in mean pressure cannot be neglected and may in some cases account, in part at least, for the occurrence of anginal pain. On the

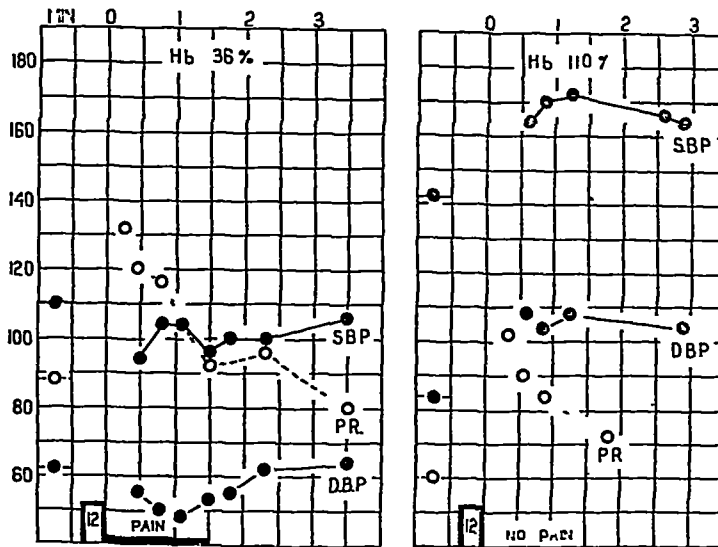


Fig 4 (Case 21) Shows the effect of twelve efforts which produced sternal pain when the hæmoglobin concentration was 36% and no pain when the hæmoglobin concentration was 110%. Compared with the non anæmic state, the systolic and diastolic blood pressures were greatly lowered in the anæmic state, both at rest and after exercise

other hand, in other cases the alterations in blood pressure were found to be less pronounced (Fig 3) or were even in the opposite direction (Fig 1) and they are, therefore, not essential to the production of angina in anæmia.

We conclude that although in different cases different factors predominate, the main factor in the production of angina in anæmia seems to be that common to all the cases, namely, a diminished oxygen supply to the working heart muscle directly due to the diminished hæmoglobin content of the blood.

Discussion

In two anæmic patients (8 and 14) both angina and intermittent claudication were experienced on walking and both disappeared after the anæmia

had been cured. In two other anæmic patients (11 and 20) walking produced only anginal pain but exercise restricted to the limbs produced intermittent claudication. Similar exercises produced no pain in either chest or limb in these patients in the non-anæmic state. These are striking examples of the way in which both angina pectoris and intermittent claudication may appear in an emia and disappear when the anæmia is cured. We have shown that the increased liability to pain in the anæmic state is to be attributed in angina pectoris largely, and in intermittent claudication wholly, to the decreased oxygen carrying power of the blood. These facts serve to link more closely the two maladies and point to a common mechanism of causation.

Moreover they help to develop our conception of the mechanisms of these pains. To avoid repetition we shall consider here intermittent claudication, the simpler form of pain, noting, however, that the following remarks are also applicable to angina pectoris. Lewis, Pickering and Rothschild (18) brought evidence to show that the pain of intermittent claudication is due to a stimulation of pain nerve endings in the tissue spaces of the muscles by a chemical or physico chemical change, termed for convenience factor P, which is stable during circulatory arrest. Factor P is in itself the result of some process, probably metabolic, occurring in the muscle fibre during exercise. They showed that while the process within the muscle fibre is determined by the amount of exercise and is largely independent of the state of the circulation, factor P only accumulates in the tissue spaces to a level adequate to excite pain when the circulation is partly or completely interrupted.

In this paper we have provided evidence that the occurrence of muscular pain during exercise with free circulation in the anæmic patient is due not to an inadequate bloodflow but to an inadequate oxygen supply to the active muscles. Since as Lewis, Pickering and Rothschild (18) showed factor P is not simple oxygen lack, it seemed to them probable that factor P represents the accumulation of chemical products formed during muscular contraction. The suggestion is that these are products ordinarily removed by oxidation. A similar suggestion has already been made by Kissin (13), to explain the appearance of pain during exercise in normal subjects breathing air deficient in oxygen. The suggestion can be easily tested. If after pain has become intolerable during exercise with arrested circulation, exercise is stopped and the circulation released, the time taken for the pain to disappear represents the time taken for the fresh blood entering the limb to reduce factor P below the threshold for pain. If factor P is removed by oxidation and not by diffusion then this time ought to be lengthened by reducing the oxygen supply without reducing the bloodflow. Reference to Table II shows that in 3 cases (1, 8 and 10) the pain disappeared after circulatory release more slowly when the patients were anæmic than when they were not. In the remaining cases the duration of the pain after circulatory release was short and was not materially affected by the oxygen capacity of the blood. To test this matter further, we have in 3 normal

subjects arrested the circulation to a limb and exercised the latter until intolerable pain was produced. Exercise was stopped, the circulation released, and the time taken for the pain to disappear determined. These observations were made with the subjects breathing room air and repeated with the subjects breathing a mixture of nitrogen and 8.5 or 10% oxygen. From Table V, which records the results, it may be seen that the pain took

TABLE V

Shows the time taken for pain to disappear from the resting limb after circulatory release in 3 subjects breathing air or an oxygen nitrogen mixture. The pain had in each case been brought to the intolerable point by exercising the limb with its circulation arrested

Subject	Gas	R arm	L arm	R leg	L leg
K	Air	4	5†	9*	7
	10% O ₂	5	15†	12*	9
P	Air	5	5†	—	5½
	8.5% O ₂	5	11†	—	8
W	Air	5	9†	10*	8
	10% O ₂	8	13†	14*	8

*Pressure in cuff reduced to 100 mm Hg at circulatory release

†Pressure in cuff reduced to 90 mm Hg at circulatory release

only a second or two longer to disappear when anoxæmia was present than when it was absent. If P factor is removed by oxidation, then it is clear that in these observations the oxygen supply has not been reduced sufficiently to delay the process materially, presumably because the flow of blood into the muscles is too great. We, therefore, repeated the observations on the normal subjects breathing air and air deficient in oxygen, but after the end of exercise the circulation was incompletely released, the pressure in the armlet being dropped abruptly from 180 to 90 or 100 mm Hg. It is to be noted that when air deficient in oxygen is breathed, the blood pressure rises and we may, therefore, assume that the inflow is less curtailed by this partial release than when ordinary air is breathed. Nevertheless in these circumstances the disappearance of the pain is slightly but definitely delayed by anoxæmia (Table V). We conclude, therefore, that factor P is normally removed mainly by oxidation.

Before continuing our main argument we wish to refer to two further points arising out of these observations. In the first place, the differences in the times of disappearance of the pain produced by varying the oxygen content of the arterial blood are surprisingly small, and it seems likely that the bloodflow through the muscles may be so great after the end of exercise that even in the anæmic or anoxæmic state the supply of oxyhemoglobin is adequate to remove factor P very quickly. Support for such a view is given by the recent work of Anrep, Blalock and Samaan (1) who believe they have shown that during actual contraction the bloodflow through the skeletal

muscles is reduced, presumably by compression of the vessels, they, like others before them, found a great increase in blood flow to follow contraction. In the second place, although we have concluded that the pain is due to the accumulation of a metabolite normally removed by oxidation, our observations on anaemia are consistent with another explanation. The pain may be due to an increased hydrogen ion concentration in the tissue spaces as a result of the diffusion out of the muscle fibres of a metabolite such as lactic acid, for the main buffer systems of the blood, depending as they do on the presence of haemoglobin and the dissociation of oxyhaemoglobin, will be reduced in anaemia. This argument applies less strongly to experiments in which the oxygen content of the arterial blood is diminished while the haemoglobin content is normal, we prefer, therefore, to emphasise the oxidative process.

To continue our main argument, we have shown that the oxygen supply to the heart and skeletal muscles plays an important part in the production of the pain of angina pectoris and of intermittent claudication. We now turn to consider why these complaints should appear in some but not in all grossly anaemic patients.

It may be recalled that angina pectoris persisted, though it was induced less easily, in two patients after cure of their anaemia, and in them it was concluded that the coronary arteries were narrowed by disease. This suggests as a first possibility that angina pectoris only occurs when there is some disease of the coronary vessels, and that anaemia, by lowering the oxygen supply to the heart still farther, reveals a permanent limitation of coronary blood flow that would be unsuspected in ordinary circumstances. A similar idea was first put forward by Herrick and Nuzum (11). This possibility can be decided ultimately only by postmortem examination, and such material as has been reported indicates that it is the true explanation in some, but not in all, cases of angina pectoris in anaemia. Thus there are at least five cases described (Cabot (3), Willus and Giffin (30), Elliot (8)) in which no changes in the coronary vessels were found postmortem. In our series, the youngest cases of undoubted angina pectoris were 37 and 43 years old respectively, and it is possible that even these had some limitation in coronary flow due to disease of the vessels.

A similar condition of early disease of the limb vessels might also explain the occurrence of intermittent claudication in anaemia. It was to investigate this possibility that we compared the effects of exercising the limbs under controlled conditions in four patients who had, and four patients who had not, experienced intermittent claudication (Divisions A and B, Table II). Of those patients who had experienced pain on walking, Case 11 was peculiar in developing unusually severe pain during exercise with free circulation in the non-anaemic state, thus, although there were no direct signs of arterial disease, it is possible that structural changes had occurred in vessels supplying muscles of the limbs. In the other three patients who had experienced pain on walking there was no evidence, direct

or indirect, of vascular disease. Thus they behaved as normal subjects in the non-anæmic state, and in the anæmic state developed pain during exercise with free circulation no more readily than did those anæmic patients who had experienced no intermittent claudication. The essential difference between the anæmic patients who had and those who had not experienced muscular pain on walking was not the presence of structural disease in the former and its absence in the latter, but simply that the latter had never walked sufficiently far or sufficiently quickly to induce the pain, enquiry revealed that they were stopped earlier by breathlessness, giddiness, or anginal pain.

The anæmic patient may be stopped by one of four events, breathlessness, giddiness, angina or intermittent claudication. If the coronary arteries or limb vessels are diseased the relevant event will be angina or intermittent claudication, if they are not, then it will probably be breathlessness or giddiness. But in some patients, for a reason that is not yet at all clear, breathlessness and giddiness seem to be less easily induced, and exercise may be carried to the point of producing angina pectoris or intermittent claudication, even in the absence of local disease of the vessels.

A note on the electrocardiographic changes in anæmia

Anoxæmia due to a diminished oxygen content of the arterial blood is known to give rise to a variety of changes in the electrocardiogram. Defects in conduction have long been recognised (Lewis and Mathison (17), Mathison (20)) and more recently attention has been drawn to alterations in the level of the *RT* segment of a type similar to those observed in coronary thrombosis (Dietrich and Schwiegk (7), Kountz and Hammouda (14), Rothschild and Kissin (25)). It is therefore rather surprising that even severe anoxæmia due to diminished hæmoglobin content of the blood should be attended by so little change in the electrocardiogram. Thus no electrocardiographic changes were found by Reid (22) in 20 cases of pernicious anæmia, nor by Willius and Giffin (30) in 12 cases of pernicious anæmia, nor by Smith (26) in several cases of pernicious anæmia and microcytic anæmia. The last observer also noted no change when the anæmia had been cured.

We have examined the electrocardiograms from ten of our cases of severe anæmia. In one (Case 19) with angina pectoris which persisted after cure of the anæmia there was left ventricular preponderance. In two cases the *PR* interval was longer than normal when the patient was anæmic and was within normal limits after cure of the anæmia. Thus in Case 20 the *PR* interval was 0.265 sec. when the hæmoglobin content of the blood was 33% and fell to 0.19 sec. when the hæmoglobin content was 97%. In Case 21, the corresponding figures are 0.205 sec. at a hæmoglobin content of 38% and 0.145 sec. at a hæmoglobin content of 110%. In the other cases no abnormality was noted during the anæmic state. Curves taken

immediately after the end of the exercise in three anæmic cases (7, 13, 17) showed no changes in the shape of the *RT* segment nor any change other than those directly attributable to exercise alone

SUMMARY

1 Pains clinically indistinguishable from those of intermittent claudication and angina pectoris may occur in any type of severe anæmia. Of 25 consecutive ambulatory cases of severe anæmia, 7 complained of pain in the legs and 8 of pain in the chest induced only by exercise and relieved by rest. After cure of the anæmia only one patient experienced pain in the legs and two pain in the chest.

2 In 9 grossly anæmic patients, exercise of the limbs without circulatory arrest produced severe pain having the characteristics of intermittent claudication. After cure of the anæmia similar exercise produced no, or only slight pain.

3 After a given amount of exercise, bloodflow through the active muscles is at least as great in the anæmic as in the non-anæmic state.

4 It is suggested that the stimulus which produces the pain of intermittent claudication is an accumulation in the tissue spaces of metabolites normally removed by oxidation.

5 In 6 severely anæmic patients complaining of sternal pain or tightness on walking the sensation was reproduced by exercise tests. In 4 patients the same exercise no longer produced pain or tightness when the blood contained more than 50% of hæmoglobin. In 2 patients the exercise tolerance increased with rising hæmoglobin content of the blood but pain could still be induced when the blood was normal.

6 The reaction of heart rate and blood pressure to exercise is usually altered in anæmia, and such alterations may contribute to the development of anginal pain. It is concluded however that the essential factor in the production of anginal pain is a diminished oxygen supply to the working heart muscle.

7 These observations support the view that angina pectoris and intermittent claudication are due to similar mechanisms operating in the heart and skeletal muscles.

8 Reasons are given why some, but not all, anæmic patients complain of angina or of intermittent claudication.

9 No electrocardiographic changes characteristic of myocardial anoxæmia were detected in anæmic patients after exercise. In 2 patients the *PR* interval was abnormally long in the anæmic state and was within normal limits after cure of the anæmia.

CASE RECORDS *

CASE 4 Hæmorrhage from piles

History Nov 1931 F.T., a tram driver of 33 years, has been increasingly breathless on exertion for 8 weeks and has suffered from headaches in the evenings. He also noticed that when walking his legs ached, particularly in the calves. On walking up a hill near his home, the pain in his legs lately became so severe that he had to stop and lean against a wall for a few minutes until the pain disappeared, afterwards he walked on until again stopped by pain. He never had this pain in his legs until 6 weeks ago and has only experienced it while walking. He has had no ache in the chest. He has suffered from hæmorrhoids for years and during the last few weeks has lost a great deal of blood from them.

Examination He is pale. Piles are present but otherwise nothing abnormal is detected. Radial and ulnar arteries are palpable at the wrist. Femoral, popliteal and posterior tibial pulses are easily palpable on both sides. The dorsalis pedis arteries are palpable with difficulty but the lateral malleolar arteries are unusually large. The reactive hyperæmia test is normal on both legs. A fractional test meal shows the presence of HCl. The stools contain no occult blood. A blood examination is as follows—W.R. negative R.B.C. = 2,900,000, Hb = 30%, C.I. = 0.51, W.B.C. = 6,000.

Progress Treated with iron and ammonium citrate 90 grains (6 gm.) daily the hæmoglobin percentage rose to 84% on Nov. the 27th. Occasional small bleedings took place from the hæmorrhoids until treated by injections. On 16.12.32, a month after discharge from hospital (R.B.C. = 5,300,000, Hb = 86%), he reported himself free from pain in his legs even during severe exercise, and also free from breathlessness and headache.

CASE 8 Chronic microcytic anæmia

History Mar 1933 I.S., a woman of 39, suffered when 26 from secondary anæmia from which she recovered after treatment with iron and arsenic. Her present illness dates from her 5th confinement 13 months ago, which was normal and unaccompanied by excessive loss of blood. Her periods have since been at normal intervals and not excessive. Her chief complaint is of increasing breathlessness and palpitation on exercise. For the last few months she has noticed a feeling of tightness in the centre of the sternum, brought on by exercise and disappearing quickly on sitting down. She has also noticed that when walking quickly or going upstairs she experiences an ache in the front of both shins, which disappears quickly if she sits down. Both the tightness in the chest and the ache in her legs are induced only by exercise, but they are never severe, and it is always breathlessness which limits her activity.

Examination shows a well nourished but pale woman, the tongue is glazed, the nails brittle and cracked. The cardiac impulse lies in the 5th interspace 14 cm. from the midline. There is a late diastolic rumbling murmur and thrill at the apex and a systolic murmur at the base. The neck veins are not engorged. The liver edge lies 3 cm. below the right costal margin, and the edge of the spleen descends 2 cm. below the left costal margin in full inspiration. The limbs are well nourished, and good pulsations can be felt in the posterior tibial, dorsalis pedis and lateral malleolar arteries of both sides. The reactive hyperæmic test is normal on both legs. No abnormal physical signs are found in the lungs or central nervous system. A fractional test meal shows achlorhydria. Examination of the blood on 21.3.33 shows R.B.C. = 2,920,000, Hb = 27%, C.I. = 0.46, W.B.C. = 9,350.

Progress Treated with Bland's pills 90 grains (6 gm.) daily the hæmoglobin rose to 60% on 29.5.33, after which it remained stationary until 0.7 gm. copper sulphate was given daily from 13.6.33, the hæmoglobin reaching 70% on 20.6.33 when she was discharged. At this time (20.6.33) she was walking considerable distances without pain in the legs or chest and without breathlessness.

Summary of investigations on angina pectoris On March the 20th 1933 (Hb = 30%) 14 efforts in 2 minutes produced in the chest a sense of constriction which lasted 1 minute 5 seconds after she sat down. This exercise altered her blood pressure to 140 mm. Hg systolic and 40 mm. Hg diastolic and her heart rate to 174 per minute (registered electrocardiographically) from resting values of 110/60 and 100 respectively.

On June the 22nd 1933 (Hb = 70%), 14 efforts in 2 minutes produced no subjective phenomena and altered the blood pressure and pulse rate to 124/74 and 108 from resting values of 108/76 and 80 respectively. On the same day, 100 efforts in 10 minutes altered the pulse rate to 160 and the blood pressure to 150/72 without producing any abnormal sensation in her chest.

* We wish to express our thanks to Professor Elliott, Dr. Bolton and Dr. McNee for allowing us to investigate patients under their care.

shows RBC = 2 280 000, Hb = 48%, CI = 1.04, WBC = 3,100 The mean diameter of the red cells is increased The electrocardiogram is normal

Progress Treatment with intramuscular injections of campolon and Blaud's pills raised the hæmoglobin to 88% on 20.2.34

Summary of investigations on angina The exercise tolerance at different hæmoglobin concentrations is given in Table IV The results of representative tests in the anæmic and non anæmic states are given with pulse rate and blood pressure readings in Fig 3 The rate of exercise was maintained at 8 to 9 efforts a minute in all the tests Nitroglycerine 1/50 grain (1.3 mg) by mouth had no effect on exercise tolerance at Hb = 50% and Hb = 84% Inhalation of amyl nitrite reduced the duration of pain from 115 sec (control test) to 43 sec at Hb = 88% Atropine sulphate 1/50 grain (1.3 mg) intravenously at Hb = 84% reduced the exercise tolerance from 33 efforts (control test) to 18 efforts, and increased the duration of pain from 125 sec to 200 sec

CASE 14 Chronic microcytic anæmia

History Jan 1933 A.T., a married woman of 46 has noticed for 6 months that when she walks quickly up hills or stairs her legs ache and feel tired She usually slackens her pace and this prevents the ache from increasing, if she stands still the ache disappears quickly The ache is brought on only by exercise, is felt simultaneously in both legs, and is confined to the anterior and posterior tibial muscle groups During the last month she has noticed that when she hurries for a 'bus she experiences in addition to the pain in her legs a dull ache situated behind the lower end of the sternum this is continuous does not radiate and is associated with breathlessness and a choking sensation, it occurs only on exercise and disappears quickly if she stops She has experienced increasing breathlessness on exertion for 6 months She knows of no abnormal loss of blood other than an excessive menstrual loss for about 6 months

Examination Shows a well nourished woman, pale but without icterus The tongue is smooth and shiny, the nails are flattened and brittle The spleen is palpable 3 cm below the left costal margin The heart is slightly enlarged to percussion (left border, 11 cm from mid line) there are no signs of valvular disease or of congestion of the neck veins No abnormal signs are elicited in the lungs or central nervous system The pulses beat normally at wrist and ankle The reactive hyperæmia test on the legs is normal A fractional test meal shows no free HCl Examination of the blood (9.1.33) shows W.R. negative RBC = 3,760 000, Hb = 40%, CI = 0.54 WBC = 5,800 The red cells show anisocytosis and a mean diameter less than normal

Progress Treated with Blaud's pills 60 grains (4 gm) daily, the hæmoglobin rapidly rose to 87% on 17.2.33 Seen on 8.5.33 (Hb = 86%) 3 months after discharge, she reported that she experienced no breathlessness and no pain in the legs or chest on exertion, though she was doing more work than before admission to hospital

Summary of investigations on angina On 11.1.33 (Hb 40%) 64 efforts in 8½ minutes produced an ache in the legs but no pain in the chest, exercise being stopped through dizziness

CASE 19 Pernicious anæmia

History April, 1932 A.W., a postman aged 57, two years previously became easily tired and breathless on exertion and experienced a pain in the centre of the chest whenever he pushed his bicycle uphill He was admitted to hospital in December 1930 and examination of the blood showed Hb = 70%, RBC = 2,710 000, CI = 1.3 WBC = 7 000 Complete achlorhydria was present His hæmoglobin rose rapidly to 100% on treatment with liver and he returned to work in February, 1931 Pain in the chest was still felt on severe exertion He did not take sufficient liver and gradually became more breathless and suffered pain more easily on exertion and was readmitted to hospital The pain in the chest is now his main complaint It arises only on exertion, is felt behind the sternum and radiates over the precordium It is continuous and passes off in a few minutes when he rests

Examination He is pale The tongue is smooth and fissured The spleen is not palpable He becomes very breathless on exertion The heart shows no clinical signs of enlargement or of a valvular lesion Apart from brisk tendon reflexes in the legs no abnormal physical signs are elicited in the nervous system Examination of the blood (14.4.32) shows Hb = 50%, RBC = 1,800 000, CI = 1.4 WBC = 4 700 The red cells show anisocytosis and polychromasia The Van den Bergh test gives a positive indirect reaction The Wassermann reaction is negative X-ray examination shows a heart of normal size with a prominent aortic notch and peribronchial fibrosis of the lungs The electrocardiogram shows left ventricular preponderance

Progress Treated with ½ lb raw liver daily from 15.4.32 the hæmoglobin rose to 90%, on 10.5.32 After leaving hospital he retired from work and no longer had attacks of anginal

pain. He was stopped when he walked by stiffness in the legs, and complained of "pins and needles" and of numbness in the hands and arms. Again he failed to continue treatment and was readmitted in March 1933 with Hb = 45%. He now had definite spasticity of the legs, the vibration of a tuning fork was not felt at the ankles. Although the anemia responded to injections of campolon, the spasticity of the legs persisted and subsequently progressed.

Summary of investigations on angina. On 2 2 32 (Hb = 60%) the resting blood pressure was 124/71 and pulse rate 80. Pain was consistently brought on by 10 efforts at a rate of 15 a minute and lasted about 1 minute 20 seconds. The blood pressure rose to 198/90 and the pulse rate to 132. Similar results were obtained on 18 2 32 at Hb = 65%, 10 efforts at a rate of 12 a minute producing pain. Nitroglycerine 1/50 grain (1.3 mg) had no effect on exercise tolerance or pain. Inhalations of amyl nitrite did not affect the duration of the pain. Atropine sulphate 1/50 grain (1.3 mg) given intravenously had no effect on exercise tolerance or pain. Carotid sinus pressure diminished slightly the duration of the pain. The exercise tolerance increased rather irregularly as the anemia improved and on 18 5 32 (Hb = 90%) 22 efforts at a rate of 13 a minute produced pain which lasted 30 seconds. The pulse rate and blood pressure rose to 127 and 165/92 from resting levels of 80 and 118/75 respectively. On 19 9 32 (Hb = 90%) 78 efforts at a rate of 12 a minute produced no pain, the patient stopping from stiffness of the legs; the pulse rate and blood pressure rose to 132 and 165/80 from resting levels of 84 and 115/75 respectively.

CASE 20 Recurrent haematemesis

History. Oct., 1923 C.L., a painter aged 59, in May, 1929, suddenly vomited about three pints of dark fluid and subsequently passed black motions. He noticed that when he was well enough to walk he was stopped by breathlessness and a pain in the chest which passed off on resting (recorded in note taken 2 10 29). In September, 1929, he again vomited copiously and was admitted to hospital. He was severely anemic (Hb = 21%, C.I. = 0.43, R.B.C. = 2,250,000) and much occult blood was present in the stools. After two blood transfusions his haemoglobin rose to 50%. X-ray examination revealed no abnormality of the intestinal tract. He returned to work and was free from complaints until July 1930 when, having vomited blood he was again admitted to hospital. His stools contained altered blood. Examination of the blood showed Hb = 62%, C.I. = 0.9, R.B.C. = 3,250,000. Again no evidence of a lesion of the stomach or duodenum was revealed by X-ray examination. He rapidly improved and was well until February 1932 when he was admitted to hospital after a haematemesis. Examination of the blood showed Hb = 45%, C.I. = 0.86, R.B.C. = 2,840,000. After two months stay in hospital his haemoglobin had risen only to 50%. He managed, however, to return to work and did not feel especially unfit. In January 1933, he again had a small haematemesis and subsequently complained of shortness of breath and pain in the chest on exertion. This pain is now his chief complaint. It is a continuous pain and is situated behind the sternum at the level of the 2nd rib and does not radiate. It is brought on only by exercise and passes off when he rests. If he walks for 50 yards as quickly as he can the pain always comes. He has never experienced pain in the legs.

Examination. There are no signs of cardiac enlargement. No murmurs are present. Abdominal examination reveals no abnormality. Normal pulsations can be felt in the dorsalis pedis and posterior tibial vessels on both sides. The ankle jerks cannot be elicited but no other abnormality is found in the nervous system. X-ray examination shows no cardiac enlargement, and no lesion of the stomach or duodenum. A fractional test meal shows free acid. Examination of the blood on admission shows Hb = 37%, R.B.C. = 4,700,000, C.I. = 39, W.B.C. = 8,700.

Progress. He was given 120 grains (7.8 gm) Blaud's pill daily and the haemoglobin rose to 90% in December, 1933, when he was discharged. Since then he has returned to work, remained well, and had no pain in his chest even after quite severe exertion.

Summary of investigations on angina. Three representative results showing pulse rate and blood pressure readings are given in Figs 1 and 2. At Hb = 37% pain was brought on by 11, 16 and 16 efforts, at a rate of 6.5 per minute, in three consecutive tests. Nitroglycerine 1/50 grain (1.3 mg) had no effect on the exercise tolerance. At Hb = 55% no pain was brought on in two tests by 36 and 18 efforts at a rate of 7 a minute, nor after atropine sulphate and 28 efforts. At Hb = 85% no pain was brought on by 100 efforts at a rate of 8 a minute.

CASE 21 Pernicious anaemia

History. November, 1933 C.L., an opal miner, aged 61, five years ago had several attacks of severe pain in the 2nd and 3rd left intercostal spaces running up to the left shoulder and down the left arm as far as the fingers. The pain arose sometimes after exertion and sometimes at rest. It was a "heavy" continuous pain, lasting for four or five minutes. After a complete rest the attacks ceased. He remained free from pain for 2½ years although he was working hard for part of the time. About a year ago the attacks recurred, coming on usually after exertion but also if he became unduly excited. The pain is now brought on by slight

exercise and passes off when he rests. It starts just to the left of the lower sternum and passes sometimes to the left shoulder and occasionally down the left arm. He has recently felt very weak and breathless on taking exercise. He has felt no pain in the legs on walking.

Examination. He is pale and there is slight icterus of the conjunctivæ. The spleen is not palpable. The heart is not enlarged and there are no signs of a valve lesion. There are no abnormal physical signs in the nervous system. Examination of the blood (22.11.33) shows RBC = 1,400,000 Hb = 34%, CI = 1.2 WBC = 4,400. The mean diameter of the red cells is increased. The Van den Bergh test shows an indirect positive reaction (2 units). There is no occult blood in the stools.

Progress. He was treated with daily injections of campolon for three weeks and then with fluid extract of liver. The hæmoglobin rose to 96% on 10.1.34 and 110% on 7.2.34. He has experienced no pain in his chest on exertion since leaving hospital at Christmas, 1933.

Summary of investigations on angina. Two representative results with pulse rate and blood pressure readings are shown in Fig. 4. At Hb = 36% pain lasting for 45 seconds was brought on by 12 efforts at a rate of 80 a minute. At Hb = 43% 45 efforts at a rate of 77 a minute did not produce pain, nor did 36 efforts at 10 a minute at Hb = 64%.

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OBSERVATIONS UPON MALADIES IN WHICH THE BLOOD
SUPPLY TO DIGITS CEASES INTERMITTENTLY OR PER-
MANENTLY, AND UPON BILATERAL GANGRENE OF DIGITS,
OBSERVATIONS RELEVANT TO SO-CALLED "RAYNAUD'S
DISEASE"*

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General comment

ONE purpose of the present paper is to present evidence for the belief that several or many quite distinct maladies are at present grouped under the single term "Raynaud's disease". The term "Raynaud's disease" has not been defined, and probably cannot be defined to obtain general agreement, strictly speaking we should mean by Raynaud's disease the disease that

* Work undertaken on behalf of the Medical Research Council

if not spontaneous, could easily be induced by warming or rubbing the part. The discoloration was always the result of exposure to cold, never of emotion. There were no instances of necrosis or of other nutritional disturbance in the digits. Enquiries showed the onset to be at or before puberty in a large majority, but the precise age of onset, if it is before 7 years, is rarely remembered with certainty. Usually the attacks were reported to have increased in severity for a few winters, then to have become stable or in some cases to have declined. In Table I the cases are divided according to whether the attacks were very rare, occurring only in extreme circumstances, such as is provided by prolonged outdoor bathing ($\frac{1}{2}$ hour or more), or were commoner, occurring not infrequently while out of doors without gloves or while dressing in cold rooms in wintry weather. This division is convenient but quite arbitrary, for there is no real boundary, brief descriptions of Cases 1 and 2 illustrate the first and of Cases 3 and 4 the second group.

Case 1 E S D, a medical student aged 20 had noticed, as long as she could remember, that after swimming in cold water for half-an-hour or more her fingers would become blanched and numb over the distal phalanges, recovery occurred spontaneously on coming out of the water and was associated with "pins and needles" in the fingers. The attacks were uncommon, occurred only after bathing, and then only if the water was cold. Her brother was similarly affected.

Case 2 J A V, a medical student aged 23, had noticed, as long as he could remember, that when bathing in cold water the distal phalanges of the index and middle fingers of both hands would become white and numb. Colour and sensation returned to the fingers about 15 minutes after coming out of the water, and the affected fingers then tingled. The attacks were infrequent but were occasionally experienced if the hands were exposed out of doors in cold weather. His sister was similarly affected.

Case 3 Nurse W, 26 years of age, had noticed for 4 years that whenever her hands were exposed on a cold day, the fingers would become numb and white, the left ring finger to its base, the others to the proximal interphalangeal joints. When warmed they would recover and tingle. The attacks were never sufficiently severe to inconvenience her, and occurred in winter only. An aunt, her only living relative, was similarly affected.

Case 4 J D, a medical student of 24 years, had suffered from "dead fingers" as long as he could remember. The attacks usually occurred while dressing in the morning, began in the right third finger and involved successively the right second, and fourth, and the left second, third, and fourth fingers. The attacks consisted of pallor and numbness beginning at the finger tips and spreading as far as the interphalangeal joints, the nail becoming violet. When warmed they would recover and tingle. The attacks occurred almost daily in winter, rarely in summer, and were induced by cold only.

It will be noted in Table I that the common history is of very infrequent attacks, occurring under exceptional circumstances, and that in this group

males and females are equally affected. Instances in which attacks are experienced more frequently, namely, on wintry days, appear to be commoner in women than in men. No difference in incidence was found according to occupation, nurses and women doctors suffering equally. Observations showing the influence of heredity will be discussed at greater length.

TABLE I
(Number of cases and percentage)

	Male	Female
Raynaud's phenomenon rarely	12 (20%)	11 (18%)
Raynaud's phenomenon frequent on wintry days	3 (5%)	7 (12%)
Raynaud's phenomenon never experienced	45 (75%)	44 (70%)
	60	62

Heredity. Among past records of "Raynaud's disease" there are occasional references to the malady as a family affection, usually a single relative—parent or child, is named, sometimes, as in Colman and Taylor's account (7), other members of the family appear to have displayed similar phenomena. The frequency with which Raynaud's phenomenon occurs in several members of the same family has not been recognised. Thus, of the 33 subjects of Table I who gave a history of Raynaud's phenomenon no less than 16, when asked, spoke of a similar phenomenon in one or more members

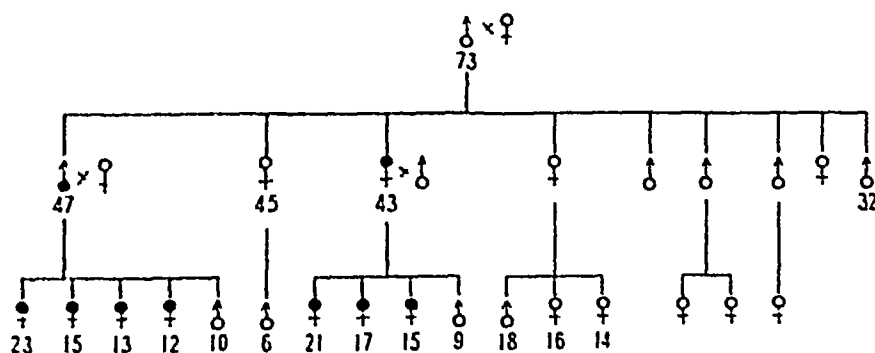


Fig. 1. Family A. Those exhibiting the Raynaud phenomenon are shown as black circles, the remainder as white circles.

of the family. Thus the simple type of Raynaud phenomenon seems to occur in more than one member of the family as often as not. This is so in part owing to coincidence resulting from the frequency of Raynaud's phenomenon in young people. We attribute it in chief part to Raynaud's phenomenon being an inherited peculiarity, this is also strongly suggested by separate observations on two working class families now to be described.

Family R In this family, shown in Fig 1, 1 male and 8 females are known to have been affected. Each of these displayed the characteristic Raynaud phenomenon, a statement based upon interviews with each individual. The attacks were brought about in each instance by exposure to cold, in only one instance was excitement said sometimes to be contributory. In none was hæmoglobinuria a complication, migraine was or had been present in the two affected members of the senior generation, but in no others. In all, the arteries of the hand and foot pulsated freely, in none was sign of sclerodactyly or of necrosis found. In all 4 sisters of the family on the left in the chart, characteristic attacks were actually induced by immersing the hands in water at 15°C in a cool room (12° to 15°). The fingers were affected, as is usual, from their tips with gradual spread towards their bases.

The following are brief notes of the individual cases

Case 5 A R, an engineer, aged 47, had noticed since boyhood that his fingers would become numb and waxy white in cold weather, his toes also were affected while bathing. Warming discoloured digits reddened them and restored sensation, with tingling. The attacks had become no more frequent or severe with time, and did not inconvenience him.

Case 6 Mrs W, aged 43, had noticed attacks of white numb fingers, but not toes, on exposure to cold for one year.

Case 7 A R, a proof reader, aged 23, stated that from the age of 7 her fingers would become waxy to their bases and numb on exposure to cold. Her toes and the soles of her feet were similarly affected. Warming these parts when discoloured reddened them and restored sensation, with tingling and sometimes sickening pain. The attacks were very frequent and interfered with her work.

Case 8 H T, a schoolgirl of 15 years, had noticed her fingers become slate blue and later white to their bases and numb during exposure to cold. The fingers reddened and became painful when warmed. The attacks were frequent in winter, and occasional in summer while swimming. Her toes were similarly affected.

Case 9 A R, a schoolgirl of 13½ years, had noticed attacks of numb and either white or blue fingers in cold weather and in summer while bathing, from her 12th year. The fingers recovered with the usual reddening and tingling when warmed or rubbed. Menstruation began at 13 years.

Case 10 D R, a schoolgirl of 12 years, complained that from the age of 10 her fingers and toes became numb and blue or white when exposed to cold. The attacks were frequent, were sometimes contributed to by excitement, but never occurred in summer, except while bathing in cold water. Menstruation had not begun. In this subject and in Cases 7 and 8, after immersing the hands in water at 43°, all the finger tips presented capillary pulsation, indicating that the digital arteries were free from structural disease.

Case 11 C W, a typist aged 21 had noticed that her fingers, but not her toes, would become numb and blue and later white in colour during cold weather, from her 14th year onwards. Her fingers recovered when warmed.

Case 12 M W, a schoolgirl of 17 years had suffered from attacks of white and numb fingers and toes in cold weather from her 14th year. Her fingers recovered when warmed.

Case 13 D W, a schoolgirl of 15 years had experienced attacks of white numb fingers in cold weather from her 12th year. Her toes were unaffected.

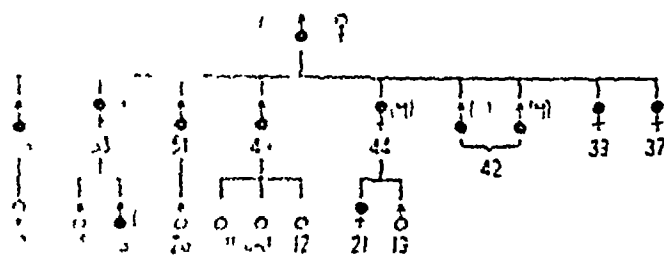


Fig. 2. *Family B.* Individuals experiencing the Paynaud phenomenon are shown in black, remainder in white. (M) signifies that the individual suffered from paroxysmal headache, probably migraine.

Family B. Of this family, shown in Fig. 2, only one member was examined. She was an intelligent woman and was interviewed a number of times, making enquiries among her kin to refresh her memory or to increase her information. She stated that the affection in the members of this family was precisely similar to her own. The following are brief notes of her case.

Case 11 M B, a married woman of 14 years, came complaining of paroxysmal headaches, limited to the right side and accompanied by vomiting from which she had suffered for 3 years. She stated that as long as she could remember she had suffered from "dead fingers" on exposure to cold. The attacks occurred frequently in the winter, but also in summer while dressing on a cold morning or after washing things in cold water. Numbness would attract attention first and, on examination, the nails would be found blue and the fingers white. Immersion in warm water brought recovery, with "pins and needles". The toes were similarly affected. The attacks had remained constant in degree. No sores or painful spots had appeared, there had been no visible blood in her urine, nor visual disturbances. The appearance of the patient's fingers when warm was quite normal. When cooled by exposure in a room at 15°C or by immersion in water at 15°C, the fingers became fully cyanotic, first at their tips, later to the proximal interphalangeal joints, the fingers reddened quickly when warmed by immersion in water at 35°C. The toes were similarly rendered cyanotic by exposure. After immersion in water at 43° the finger tips all presented capillary pulsation.

2 INTERMITTENT SPASM OF DIGITAL ARTERIES WITH LOCAL NUTRITIONAL CHANGES

Illustrations of this well recognised group will not be given, the type was described by Raynaud (Case 11 of his original thesis) and instances have recently been extensively investigated and reported by Lewis (23, Cases 1, 2 and 3). A brief general description will serve to emphasise points relevant to the general discussion and to bring the type into correct perspective.

The original symptoms in these cases are precisely the same as those of the last group, namely, attacks of discoloured numb digits on exposure to cold with recovery on rewarming. The fingers are more often and more severely affected than the toes, and it is to be remarked that in this and Group 1 the nose and ears are very rarely affected. The cases differ from those in Group 1 in that the condition is progressive or occurs in more serious form from its beginning, the attacks are easily provoked, occurring not only in winter but on the colder days and evenings of summer. It is not a matter of occasional and brief attacks, but of frequent and often prolonged attacks, and perhaps of intervening periods during which the circulation to the fingers recovers incompletely (the state described as "intermittent leakage" (23)).

Bloodflow to the digits of such patients is arrested or almost arrested for many hours each day in cold weather, and the affected parts, especially the fingers, nearly always show changes in their tissues. Sometimes the fingers may present a little chronic swelling, or they become marked from time to time by chilblains, modified in appearance by the defective circulation to the part. Clear evidences of atrophy are not unusual, the fingers then being narrow, tapering to their ends, the pulp of the finger diminished, and the slow growing nails ridged or increased in curvature. In such fingers it is usual for the skin of the fingers to be less than ordinarily mobile. Whether swollen or showing signs of sclerodactyly, flexion of the fingers is limited. In those cases with the more obvious changes it is the rule for areas of necrosis to appear from time to time at the finger tips, minute scales or plugs of tissue separate very slowly and painfully, leaving tiny depressed scars, or little necrotic areas with or without previous blistering come at the border of the nail and discharge a little serum or pus and heal slowly. It has been ascertained, in the more advanced cases of this group, that the digital arteries are incapable of full dilatation, these are almost certainly the seat of structural disease tending a little to obstruct their lumina.

It is to be understood that the picture here painted is of an advanced state of the malady, between this and the type described in Group 1 there is every intermediate form, it is known that patients of the first group may, but do not necessarily, pass over into the second.

The pathogeny of Groups 1 and 2

When the body and limbs of a normal subject are exposed to cold, the bloodflow through the digits becomes extremely slow, so slow that we know the arteries must be almost closed. Actual closure is, however, abnormal, and is the characteristic feature of the cases constituting Groups 1 and 2 just described. It is clear from the preceding account that there is a gradual transition from the normal subject in whom closure never occurs, to the severe case of the malady in which the arteries are shut for long periods each day in cold weather. In normal and abnormal subject alike, narrowing of the digital arteries is the resultant of two factors, increased vasomotor tone in response to cold, and the direct response of the vessels to cold. The hypothesis that the circulation can be arrested locally, thus threatening necrosis of the tissues of the digits, by simple overaction of the vasomotor nerves, has recently been attacked where it was most strongly entrenched, namely, in its application to cases of the types here considered.

Thus in the severe cases of Group 2, a long series of experiments (23, 24 and 25) has proved conclusively that the theory of vasomotor overaction is inadequate and that closure of the digital arteries is due to a local fault in the vessels. This evidence will not be reiterated here, it will suffice to recall the crucial observations, firstly that attacks of full cyanosis can be induced in the digits by exposing them to the direct action of cold after their vasomotor supply has been interrupted by a local anæsthetic or by sympathectomy, and secondly that chilling of the body fails to produce full cyanosis in a hand kept normally warm.

The nature of this local fault is still unknown. It has been ascertained for many of the cases of the type considered (those of Group 2) that the digital arteries are incapable of complete dilatation (23, 26), and there is little doubt that they are often the seat of early structural disease, though the frequency and extent of such disease has not been ascertained microscopically. Now it would be reasonable to argue that intimal thickening by narrowing the lumen sometimes causes a vessel, brought to a certain state of tone, to close prematurely, and it is possible to suggest that there is sufficient disease in certain of the cases of Group 2 to bring about closure in this manner, in that case intimal thickening might come to be regarded as constituting the local fault. But the suggestion that the local fault is usually of this nature is not at present a very acceptable one. There are reasons for doubting if early grades of intimal thickening would render a vessel impervious while in a state of high but normal tone. Moreover we are still left to explain why, given such early intimal thickening, a rise of tone due purely to nervous impulses (the vessel being kept warm) fails to close the vessel, while cold applied to the vessel does close it, even after sympathetic nerve section. These are facts of observation, and they indicate powerful response of the arterial wall to the direct stimulus of cold. Thus it seems probable that intimal thickening, as this is supposed to occur in certain of

these cases, plays but a subsidiary part, and that the local fault in the vessel wall is more properly regarded as a functional one, an overaction to the cold stimulus. It should be understood that whether intimal thickening is regarded as playing a material part or not, the disease is to be considered as an affection of the vessels and not of the nervous system.

Now, although the evidence pointing to a local fault has been obtained mainly from the severer cases of the malady, it has not been derived exclusively from them. Thus, strongly suggestive of a local vascular abnormality are the observations that when cold is applied locally it brings the circulation to a standstill only in those fingers directly submitted to its influence, and that warmth fails to restore the circulation to a finger unless applied to that finger and to its whole length. These phenomena were witnessed repeatedly in the cases of Group 2, and they have been witnessed in cases belonging to Group 1. Thus they were seen in Cases 8, 10 and 14 previously described, in all of whom the relevant tests were made. In cases of this kind the induction of attacks by local cooling, under conditions in which there is every reason to believe that vasomotor tone in other parts of the body is within normal limits, is frequently possible. Decisive identification of the abnormal factor is, however, extremely difficult in those milder cases in which the departure from normality is slight, because in such patients closure of the arteries ordinarily occurs only as a result of both the increase of vasomotor tone and the local response of the vessels to cold. Failure to produce cyanosis in mild cases by cooling the digits, after paralysing their vasomotor supply by local anaesthesia or sympathectomy, does not show that the abnormality lies in the vasomotor system. For, even if the direct response of the vessel is abnormally strong, it is to be anticipated that in the mild case Raynaud's phenomenon will be difficult or impossible to produce by local cooling when vasomotor tone is abolished. This is so because local cold, barely an adequate stimulus when vasomotor tone is normal, is inadequate when vasomotor tone is abnormally low. Nevertheless, from time to time even in cases in which there is no evidence of early arterial disease, it may be shown that loss of sympathetic tone, induced by nerve anaesthesia, fails promptly to relieve arterial spasm previously present. An instance of this kind has been described in an earlier paper by Lewis and Pickering (27, Case 2, Table IV).

Neither in cases of Group 1, nor in those of Group 2, is there evidence to warrant the supposition that during spontaneous attacks vasomotor tone is abnormally high, attempts to show that the blood pressure is raised unusually, or that the limb volume diminishes unusually in response to a general cold stimulus, have not succeeded. All the phenomena witnessed are explained adequately upon the basis of a local vascular fault. It may be that the demonstration has not reached quite the conclusive point in the case of patients of Group 1 as it has in those of Group 2, but it has gone far. There is also the general consideration that the cases of the two groups are not strictly separable and that a patient at first included in Group 1 often

comes later to be included in Group 2. There is close similarity between the attacks in the two groups of patient, in the manner of their production, in the parts affected and the order of their involvement, making it difficult to believe that there are two diseases, one in which the primary fault is local and another in which it lies in the nervous system.

If we compare in cold atmospheres, the normal subject and the subject displaying Raynaud's phenomenon in its mildest degree, we shall recognise that the difference between them is a small one. At all events this is so if the gauge is the size of the arterial lumen and not the tone of the vessel wall. The difference referred to constitutes an abnormality, which definitely tends to be familial. In the mild case, and for reasons previously stated, it is going to be a very difficult matter conclusively to decide by *direct evidence* whether what is apparently a slight departure from normality in response to cold is due to slightly higher vasomotor tone, or to a slightly greater direct reaction of the vessels themselves. So we rest at the moment upon less direct evidence and comparison. A slight departure from normality is not enough to account for the difference between the reaction to cold of a normal subject and of one who experiences serious inconvenience through relatively frequent and prolonged arrest of the digital circulation. Here there is a graver divergence from normality, and as the malady becomes more conspicuous so the evidence points more convincingly to the local vessels as the primary seat of disturbance.

3. INTERMITTENT SPASM OF DIGITAL ARTERIES WITH GENERALISED SCLERODERMA

Cases of this type have recently been discussed at length by Lewis and Landis (26) and need no new illustration. The attacks of discoloured fingers in these patients have proved indistinguishable from those of the last group, they are brought about through a local fault and not through abnormal vasomotor impulses. There are similar nutritional changes in the fingers, namely, small areas of dry necrosis or of ulceration, and hardening of the digital skin. The feature of this group is that the hardening of the skin is advanced and is not confined to digits, but appears also over the shafts of the limbs and over parts of the face and trunk.

It has been proved by observation during life and after death that the arteries of the affected regions of skin are the seat of structural changes tending to obliterate their channels. But the pathological relationship between arterial obstruction and scleroderma remains obscure. Cases of this third group have been observed to develop out of those originally classed in Group 2 or even in Group 1. The observed transition, and the knowledge that defective nutrition is followed by atrophy and may be followed by fibrosis, form arguments leading with seeming security to the linkage of digital arterial spasm as the cause, to sclerodactyly as an ultimate effect. But the transition is not invariable and, in facial scleroderma, abnormalities in the behaviour of arteries to the corresponding territories have not as yet

been demonstrated. Furthermore there are seemingly rare cases where, even in the hands, hardening of the skin noticeably precedes attacks of discoloration, and in this instance it would be quite reasonable to argue from the order of events, that fibrosis is the end of a chronic inflammation, which causes proliferative changes in the small arteries, a view consistent too with current pathological teaching. Thus two lines of reasoning would lead to almost converse conclusions, and impel us to the belief either that one or both of these lines of reasoning is wrong, or that we are in fact dealing with two different diseases superficially resembling each other closely. The position as it stands is here briefly given to display the problems which this particular type of case still presents, its provisional separation from the remaining groups is justified on this ground alone.

4 RAYNAUD'S PHENOMENON ARISING OUT OF LOCAL INJURY

Case 15 Spasmodic obstruction of the bloodflow to a finger following local injury

E A D, a medical student 23 years old, injured the proximal interphalangeal joint of the right ring finger when hitting a fives ball with his hand four years previously. At the site of the injury the finger swelled and became painful and remained so for two or three months. Some months after the injury he noticed that the two distal phalanges of this finger became waxy white in cold weather. Sensation in this finger became definitely impaired when it was white. When warmed the finger became red and sensation returned. This affection persisted for two winters and then disappeared. He never had similar trouble before the injury, and never noticed discoloration of other digits.

This is an instance of Raynaud's phenomenon arising out of a single injury, a spasmodic affection dependent perhaps upon a changed reactivity of the vessel wall to cold, or perhaps upon structural change within the vessels.

Case 16 Raynaud's phenomenon following long continued vibration

M E, was a shoemaker of 27 years, who had noticed attacks of discoloration of his fingers for 1½ years. At the time his trouble began he had been at his work for 5½ years, using a machine for modelling the shoe. He held the shoe in both hands against a rapidly revolving wheel, if the shoe was not held with considerable force against the wheel it vibrated rapidly, the vibration being felt in hands and forearms. Later he worked on a lasting machine, the shoe was held in both hands while the machine tacked the upper parts to the sole, the vibration was at the rate of about 120 per minute, and was felt by both hands, but not uncomfortably. The man who preceded him on the first machine acquired the same trouble, a worker of 60 who used the second machine was also affected.

The first of his fingers to be affected was the 3rd left, shortly afterwards the 4th left, and then the other fingers on both hands. On the right hand the 2nd finger was the first to show the change. The attacks were never

provoked by the vibration of the machine, but only by cold in the intervals of work. Exposure to cold air out of doors or immersion of the hands in cold water sufficed. The fingers would become pale, pallor beginning at the tips of the fingers and spreading up as high as the proximal interphalangeal joint, eventually the fingers would become waxy in colour and numb. When numb, the finger could touch red hot coal without sensation, but it gave burning pain on recovery. Recovery was ordinarily associated with redness and tingling.

When the man came for examination his hands were warm and of normal colour. His fingers were thick, strong, and rather short. The hands were marked equally by callosities on their palmar surfaces and especially on their radial sides. His left hand was immersed in water at 15° for 20 min in a room at 15° . The 5th finger alone became cyanotic, and this transiently. He then went out of doors (temp 9°) exposing his hands, and in 15 min returned with fingers 2, 3 and 5 of the left hand blanched, 2 and 3 to their proximal interphalangeal joints, 5 at its tip, the finger tips were insensitive to touch. Indoors the fingers rapidly recovered their normal colour. The left hand was again immersed in water at 15° , and in 5 min the same three fingers became cyanosed, the condition was however unstable.

This case is an example of an affection previously described on a number of occasions. It would appear from the accounts of Hamilton (16), Seyring (14) and Legge (21) that Raynaud's phenomenon frequently develops in the hands of those who use rapidly vibrating pneumatic chisels to clean castings, and in those of factory workers who mould shoes by means of "pounding" machines. The hands become affected after using the machines for periods of years. It is quite evident that although the affection is the result of using these machines, the attacks are not provoked in this way, it is only when the hands become cold, and this is usually when no work is being done, that attacks are experienced. The injurious factor has been sought by Seyring and recognised by him to be the vibration. It is the hand holding the vibrating end of the chisel, and the fingers nearest to this end, which suffer earliest and chiefly.

From previous accounts and from our own examination of a single case it is obvious that the attacks resemble those experienced by patients in Groups 1 and 2, they begin in the tips and spread up the affected fingers, waxy discoloration and numbness ultimately appear. Isolated instances of necrosis have been recorded, there is also the characteristic response to local cooling. Fingers of such cases have not yet been tested to discover any evidence of local arterial disease, which may be presented by them, and no opportunity has occurred of examining the arteries directly. Although the affection is clearly brought about by a local stimulus and cannot reasonably be referred to the nervous system, the precise nature of the disturbance remains obscure.

B BILATERAL GANGRENE OF DIGITS

We shall now consider cases which we believe to be of quite different type pathogenetically to any of those previously described, namely, patients who suffer from a single illness in which considerable parts of the digits are lost by a process of gangrene. For purposes of further study these cases must still be kept in a few separate classes. To simplify our account we have excluded cases of gangrene so massive as to involve the whole of hand, or foot, or foot and leg. But it is to be recognised that this exclusion is arbitrary, there is no known clinical or pathological basis for sharp separation.

5 BILATERAL GANGRENE OF DIGITS IN THE YOUNG, AND WITH INFECTION

First we shall consider gangrene of extremities in which there is no reason to suspect the previous existence of arterial disease.

Case 17 Acute and permanent obstruction of many digital arteries leading to gangrene in a young girl, the cause unknown, subsequently Raynaud's phenomenon

E P, a country bred girl, had suffered from neither infective disease nor accident before her illness. She had always eaten white or brown, but never rye, bread. Until her illness her hands had always been warm in ordinary circumstances, chilblains had never been experienced. In the late summer of 1929, when 10 years of age, and during warm weather, her fingers and toes became discoloured. At first and without warning they were red and swollen, but soon they became darker in colour and mummified. This rapidly developing dry gangrene had lasted for six months when in March, 1930, we saw this child, who was well nourished and otherwise healthy, and of bright disposition. When seen she was in bed in a cool ward. On the right hand, the 1st and 2nd fingers were of normal colour though cold. The distal halves of the terminal phalanges of fingers 3, 4 and 5 were gangrenous, the tissues being shrunken, black, hard, and dry. Above the gangrene these fingers were of deep violet colour as high as the proximal interphalangeal joints. The pulsation of digital vessels could be felt distinctly even at the end of the 2nd finger, and in the normally coloured bases of fingers 3 and 4. The left hand was less affected, the 1st and 2nd fingers were normal in colour, half the terminal phalanx of finger 3 was gangrenous, fingers 4 and 5 had been affected to a smaller extent, and the necrosed tissue had separated and the nails had regrown imperfectly. The proximal parts of fingers 3, 4 and 5 were of deep violet colour. The affected areas of the left hand remained deeply cyanotic after immersion in water at 35° for 10 min. The cyanosis persisted but was less intense after immersion of the hand at 40° for a further 10 min. All the toes of both feet were deeply cyanotic throughout their lengths, and small patches of dry gangrene were present beneath two of the nails. The whole of the end of the nose, down to but not involving the nostrils, was blue in colour and very cold in comparison with the rest of the face, the discoloured area was sharply defined, circular,

and about 2 cm in diameter. The cheeks were a little cyanotic and cool, but the ears presented no abnormality.

We were assured that the condition of fingers, toes, and nose had changed very little during a period of many weeks, and had not changed much since the early days of the malady. It was doubtful if the discoloration of the digits was continuous or discontinuous at the outset, but it was clear that the gangrene developed almost simultaneously in all the digits affected, as did the accompanying cyanosis in the more proximal parts. It was manifest that at the time the child was seen the cyanosis was stable, and not the result of a spasmodic closure of the vessels. A noteworthy feature was the sharp demarcation of normal and abnormal tissue, the pulsation of digital vessels being perceptible up to the actual border of discoloration.

There was no history of bloody urine, and after a lump of ice had been pressed against the skin of the forearm for 5 minutes the subsequent local reaction was normal.

This patient was next seen in June, 1931, at the age of 15 years. She had grown to be a tall girl in the interval of 5 years. After she was last seen the healing of her fingers continued slowly but uninterruptedly. There had been not the slightest fresh necrosis in the fingers, but during her convalescence she noticed for the first time that her fingers became white and numb in cold weather. All the fingers, except the thumbs, were affected in this way, the discoloration starting at the tips and progressing to the proximal interphalangeal joint or a little beyond. Certain of her toes reacted similarly to cold. The attacks were frequent in cold weather, occurring invariably on going out of doors on cold days. Her cheeks would also become blue, and the area of the nose previously affected would become more deeply cyanotic and cold. She thought that the attacks were gradually becoming less frequent.

On examination the fingers that had suffered necrosis were short, pulp and distal half of the nail of each having been lost. But the skin was everywhere mobile, and flexion of the fingers unimpaired. The hands were warm, but her fingers cool. As previously, the digital pulse could be felt at the base of every finger, but capillary pulsation could not be induced in any of the affected finger tips by warming the hand to 43°, though it was present in both thumbs and in the palms of both hands. When the hands were thoroughly warmed at 35°, and the circulation to the limbs arrested for 5 min and released, the subsequent reactive hyperæmia was distinctly delayed in the tips of fingers 2, 3 and 4 on the left and in finger 3 on the right side. The only part of this patient's face that was cold in a room at 22° was the end of her nose, which was at 25°, while the rest of her face was between 30.5° and 32.6°.

To sum up, this case illustrates an attack of prolonged discoloration of the fingers of both hands, and of the toes, appearing acutely and without warning, and proceeding at once to gangrene. We have not to deal with repeated attacks of discoloration coming and going for years and ultimately

leading to the formation of minute areas of necrosis of the finger tips, but with one attack, causing relatively massive gangrene and mummification of the finger ends. To ascribe the attack simply to continuous spasm of the arteries in the affected area is impossible, the attack was too prolonged, the area involved was too sharply defined and unvarying, and the vessels could not be opened by warmth or by other means, as they invariably can in all undoubted instances of spasm. The case is to be regarded as an example of sudden and permanent obstruction of the arteries, quickly causing death of parts of the tissues supplied and a permanent circulatory defect in other parts, recognisable four years later.

Case 18 Acute and permanent obstruction of many digital arteries leading to gangrene, in a young woman suffering previously from cold hands and feet, the cause unknown

G E, a shop assistant of 20 years, had enjoyed good health though her hands were cold and red in childhood and chilblains occurred on hands and feet. It had been her habit to eat white bread only, there was nothing peculiar about her diet, she did not smoke. In November, 1932, three weeks before she was seen, and without change of general health or habit, her left 2nd finger became white and numb, and a day or two later the right 2nd finger was involved. They remained white for several days and then became painful and later swollen. A few days after the involvement of the 2nd right finger, the right thumb became blue, and a fortnight later the 3rd right finger also, soon these fingers became swollen. This blueness appeared especially when the fingers were exposed to cold air or water. The 3rd and 4th fingers on the left hand became involved a week before she was seen. The white fingers became blue, and the colour of all the affected ones darkened until, by December the 1st when she was first seen, necrosis had appeared in several fingers.

She was examined while warmly wrapped up in a room at 21°. The hands were well formed and the nails smooth and small. On the right side the thumb was normal in colour but presented a small necrosis at its tip, a large and tender area of necrosis, beginning to heal, was seen along the border of the 2nd nail, under the 3rd nail was a small necrosis. Fingers 2 and 3 were cyanotic, especially at their ends. Fingers 1, 2, 3 and 4 of the left hand, and especially their tips, were also very cyanosed. It was noted that while the palms of the hands and bases of the fingers were very warm, the affected fingers were cold, and the transition from cold to warm skin was relatively abrupt (Fig 3). The radial and ulnar pulses were full and the digital arteries could be felt beating at the bases of the affected fingers of both hands. After long immersion of the hands in warm water (34° and then 40°), the affected fingers remained abnormally cyanotic, though their colour brightened a little.

On two occasions when the fingers were all cold the patient was placed in a hot chamber, the hands projecting. The last affected left 5th finger warmed up quickly and fully (to 35°), so did the bases of all the fingers but

the warming up of the tips of the more affected fingers was delayed and imperfect, the temperatures reached being only 24° to 27° . After soaking the left hand in water at 35° for 10 minutes the circulation to the arm was occluded and the arm kept immersed. On release, reactive hyperæmia flooded the

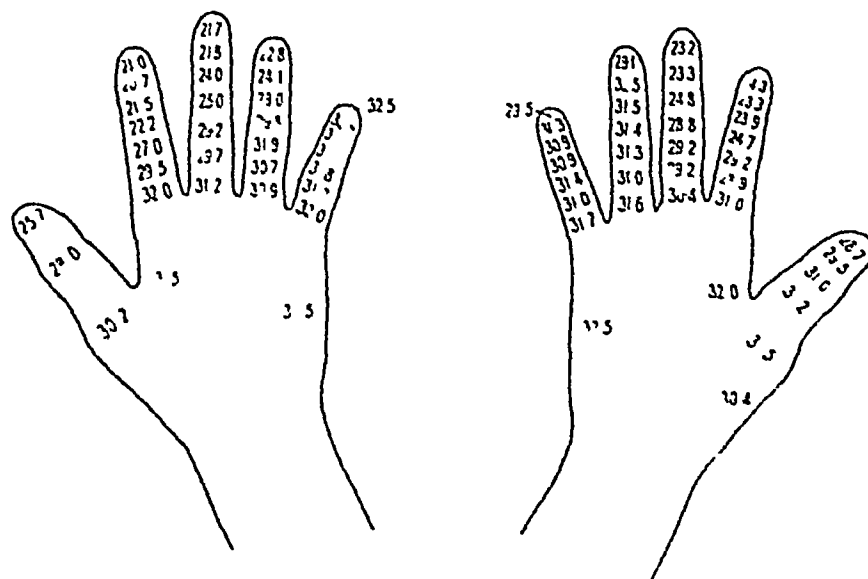


Fig. 3 Case 18 January the 5th, 1933 Thermoelectric readings of temperature of the palmar surfaces of the hands after exposure in a cool room

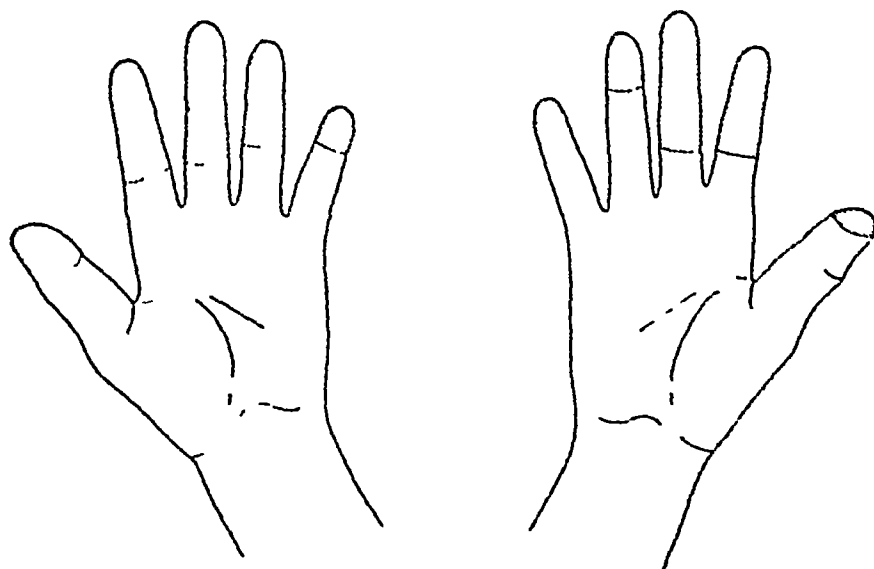


Fig. 4 Case 18 January the 6th, 1933 The areas of cyanosis appearing after immersing the hands for 15 minutes in water at 15°C

hand and fingers 1 and 5 normally, namely in a second or two, but the ends of fingers 2, 3 and 4 remained cyanotic, taking 20, 90 and 90 sec, respectively, to clear. The right hand, similarly tested, showed delayed hyperæmia of fingers 2 and 3. Immersion of the hands in water at 15° (R T 17°) gave

within 15 min a complete display of the parts affected, these becoming cyanotic as shown in Fig 4

The patient was in bed under observation for 5 weeks During this period the condition of her hands changed a little, the same fingers became blue when exposed to cold as formerly, but pain which was prominent originally in the fingers presenting necrosis, had subsided, and on repeating the reactive hyperæmia test, which has been described, the flushing of the affected fingers was less conspicuously delayed

Though cold and affected by chilblains from time to time, her feet had been normal Her face was normal Hæmaturia had never been noticed Ice applied to the skin for $\frac{1}{2}$, 1, or 5 min gave normal subsequent reactions Her general health was excellent

This patient was last seen on October the 18th, 1934 The condition of the fingers was unchanged, they became cyanosed and numb when exposed out of doors in cold weather or when immersed in water at 15° After soaking the hands in water at 45° for 10 min capillary pulsation was seen distinctly in the tips of fingers 1, 4 and 5 of the right and in fingers 1 and 5 of the left hand, in the remaining finger tips it could not be detected, these were the fingers originally showing relative coldness (Fig 3)

This case is in many ways similar to that previously described (Case 17), though the subject was a little older and gave a preliminary history of cold fingers and chilblains There was clear evidence of permanent obstruction coming on within a period of days in the arteries supplying a number of fingers on both hands, an obstruction, not by spasm, but by structural disease For the obstruction lasted too long to be spasmodic and could not be relieved by local heating, by reactive hyperæmia, or by general vasodilatation, and the areas of defective blood supply remained unchanged during a long period of observation The damage to the vessels was a lasting one

Comment The curious malady, of which these two cases form illustrations, is exemplified a number of times in past records In Table II we have incorporated examples, selected to illustrate the chief points to which we desire to draw attention Using these cases and our own it may be said that the main features of the malady are as follows It frequently attacks children or young adults Females do not seem more prone to the affection than males There is very rarely a history of previous attacks of discoloured extremities, very exceptionally there may be a previous account of chilblains The malady customarily starts without warning, several fingers or toes or both becoming discoloured within a period of several days, not infrequently the end of the nose is involved and the ears The part attacked is not affected transiently or intermittently but remains discoloured until after weeks or months it recovers colour, usually with loss of tissue at its end by a process of dry gangrene It is essentially a single attack, an illness that is unrepeatable, though there have been rare instances in which a second attack, slighter or equally severe, has come within a few months of the first The gangrene is considerable, tissue corresponding to the length of the nail or of

TABLE II

Bilateral gangrene of digits, in the young, or with infection

Author	Sex and age	Second attack	Gangrene in	Bilateral	Agency
Raynaud (70) (C. 12)	M 34		toes	one side blue only	Emaciation
Raynaud (C. 13)	I 84	1-24 m later	toes	yes	Chilblains previously
Lewis (17)	I adult		fingers, toes, nose	yes	Unknown
Meliss (28)	I 25		toes	yes	Unknown
Mell (29)	I 2	1-7 m later	toes, cheeks	yes	Unknown
Lewis (70)	I 5		toes (blue fingers)	yes	Chilblains previously
Zils (18)	M 27		fingers, toes (blue nose)	yes	Unknown
B. (2)	I 21		fingers, toes, ears, nose	yes	Recent confinement, possibly ergotism
L. Chandler (11) (C. 15)	M 12		toes	one side blue only	Typhus
(C. 17)	M 10		toes and feet	yes	Typhus (10 days)
(C. 18)	F 15		toes	yes	Typhus
Richard (11)	M 16		toes, etc	yes	Typhoid (6th week) Typhoid (10 days) } two brothers
	M 17		toes	yes	
Seidlin (13)	I 20		fingers, toes (blue ears)	yes	Pneumonia, convalescence
Dufour (9)	I 58		fingers, toes, nose and ears	yes	Pneumonia convalescence, general skin eruption
Dardignac (8)	M young soldier		fingers	yes	"Influenza"
Powell (35)	M 18		fingers, toes, ear (blue nose)	yes in fingers, one ear blue only	Throat infection, convalescence
Hutchinson (19)	M 37		fingers, toes, ears	yes	20 weeks pain in chest and exhaustion
Labin (12)	I 15	2 m later	fingers, toes (blue nose, ears, cheeks)	yes	Associated fever, skin eruption and glycosuria

one or two phalanges being lost, the necrotic tissue separates slowly and the healing may be prolonged for very many months. The digits are almost always affected bilaterally, often quite symmetrically, and parts of the ears and the end of the nose are on occasion lost. The area that becomes necrotic is less than that which is originally threatened, and deep discoloration may clear away from a digit and often does from the nose without loss of tissue. In many cases the origin of the malady is quite unknown, occurring in an apparently healthy young person in whom no pre-existing disease of vessels can be suspected, but more often there is *malnutrition* or *actual illhealth* at the time. It has been recorded during the course of acute infections such as typhoid and typhus, during convalescence from pneumonia, and in other or less clearly defined acute infections. The cases are often recorded under the accurate title "symmetrical gangrene," they are often reported as examples of "Raynaud's disease."

It is impossible to admit these cases within the groups previously discussed, namely with the spasmodic cases. It was while discussing cases of the kind that Hutchinson wrote nearly 40 years ago, "All who have studied in any detail the cases which have been grouped together under the name of Raynaud's malady will admit that the time has arrived when they ought to be classified. They are not all alike, nor do they all tend to the same results." We have come ourselves to the same belief and to agree that these cases should be separated sharply from those characterised by transient attacks of cyanosis, and we are not deterred from expressing this view by the fact that Raynaud incorporated the case displaying many attacks of discoloration and the case displaying a single attack of symmetrical gangrene in one pathogenetic category. He believed both types to be the result of spasm of the vessel wall, in support of spasm in the first he provided clear evidence, in support of it in the second he provided no positive evidence except the feature symmetry. The symmetry of gangrene was to Raynaud of much importance, as may be judged not only from his text but from the title of his main thesis, and it stood to him for an evidence of primary involvement of the nervous system. This cannot now be allowed, for symmetry is known in cases of gangrene clearly arising out of arterial disease (see Cases 19 and 20 and comments). Hutchinson (19) thought that the malady arises either because there is a severe affection of the heart, or because a poison has gained access, producing temporary closure of peripheral arteries. In either way symmetry could be explained, he was unwilling to believe in permanent and symmetrical plugging of vessels. It is here to be noted that in the case records of various authors reference is often made to the main arteries supplying the affected parts, to the popliteal vessel or to the two main arteries of the foot, and these vessels are stated to be pulsating. Raynaud's early distinction was between gangrene following disease of main arteries, and gangrene in subjects in whom the main vessels were felt to be pulsating or were found open after death, it has been assumed too readily that gangrene must be of spasmodic origin if the *main* arteries are open. The smaller arteries have

received very little attention, and it is here that our own observations are important. These have confirmed the fact that the main vessels are unobstructed, but they have brought clear evidence of obstruction in vessels of the order of the digital arteries, of obstruction above the level of necrosis in the finger, but of obstruction which is unrelievable, permanent, and therefore to be adjudged structural. Hutchinson emphasises the nose particularly, refusing to believe that plugging of its vessels can cause gangrene, yet in our own patient (Case 17) the end of the nose, which was threatened by gangrene in the initial stages of the attack, like the fingers retained the defect in blood supply for years after all signs of active disease had vanished (a similar event occurred in Faure's case (13) in Mendel's case (29) and in the fingers of our Case 18). It is difficult to imagine any other explanation to account for these facts than that the vessels were originally plugged. We conclude that the cause of circulatory obstruction in our own patients was a change in small arteries, coming abruptly and permanently closing them. An initial spasm of these vessels, the result of poisoning or other agency might conceivably have started this process, but it could not have resulted in a persistent state of obstruction. We believe, therefore, that the change was structural and, to be more specific, thrombotic. This thrombosis may have been the initial change. Conceivably, it may have occurred as a sequel to a condition of spasm, but we possess no evidence to support such an assumption.

Cases 17 and 18 of our series, and the cases of Faure and of Mendel, are of further interest in illustrating how Raynaud's phenomenon, or spasmodic arrest of circulation to digits in response to cold, may appear where there is old standing disease of the arteries to the fingers, brought about originally by an acute process.

6 BILATERAL GANGRENE WITH HÆMOGLOBINURIA FROM COLD

The relation of discoloration and gangrene of the digits or parts of the face to hæmoglobinuria from cold has been discussed in previous papers (17, and 23 page 83) from this department, in which references to cases will be found. The patients recorded have usually been males, often children, but sometimes adults. They suffer from hæmoglobinuria after exposure to cold, have experienced usually one but sometimes several attacks of gangrene. The gangrene is generally bilateral, affects the tips of the ears particularly but may also affect fingers, toes, or nose, it is usually clear that it has followed exposure to cold. Gangrene may not occur, but attacks of cyanosis (*see* Bywater's recent case (6)), or of whiteness and swelling, replace it, or gangrene and discoloration occur in different attacks in the same case. The patients are often infected congenitally or otherwise by syphilis. These cases are closely allied to instances of hæmoglobinuria with urticaria, both of which are responses to cold, this linkage is emphasised by the occasional occurrence of gangrene and urticaria in the same case. Hæmoglobinuria from cold is due to the action of a hæmolytin, urticaria from cold is due to

the action of a related dermolysin, cases displaying these phenomena are therefore of a very special kind. It has been suggested that gangrene in cases of hæmoglobinuria is due to the action of a lysin either on the skin itself or upon the endothelium of its blood vessels, leading to thrombosis in these. The peculiar clinical features of the cases of gangrene here considered and the possibility of a very special pathogeny, renders it essential that they should be kept in a category of their own.

7 BILATERAL GANGRENE OF DIGITS IN THE ELDERLY, AND WITH DISEASE OF SMALL ARTERIES

In clinical form closely resembling the types of massive gangrene just described is a form of gangrene occurring in elderly people. In these it may be associated, as the following cases show, with demonstrable disease in the arteries of the affected fingers. Therefore, it is again desirable to keep these cases separate.

Case 19. Acute and permanent obstruction of arterial supply to many fingers in an old woman, leading to gangrene, autopsy

N P, a woman of 67 years, had noticed her hands to be cold all her life, she had never experienced chilblains of hands or feet. She had been healthy, with the exception of a varicose ulcer of her right leg, which healed a year previously. Three months before admission a number of her fingers became discoloured and very tender, the fingers were affected one after another in the space of two weeks, they became steadily worse, the area of discoloration extending upwards. Discoloration was not intermittent, but persistent wherever it appeared. There had been discharge from the 2nd and 3rd left fingers. During the last weeks the pain in the fingers had been present almost constantly, there were periods of a few hours comfort and other periods of "dreadful" pain. The pain was increased by heat and relieved by cold.

On examination the metacarpophalangeal joints showed distinct swelling with slight ulnar deviation of the fingers. The fingers of the right hand were all cold, but especially fingers 1, 2 and 3. Fingers 2 and 3 were discoloured, they were covered with thick soiled skin, but despite this covering they were obviously cyanotic, the corresponding nails were short and distorted, the epithelium being heaped up beneath the free margin of each, much of the pulp of both these fingers had been destroyed by recent necrosis, both the fingers were very tender. The ulnar pulse could not be felt, the radial pulse was large and occlusion of it showed that all or almost all the blood supply to the hand was carried by this vessel. This hand was immersed in water at 41° for 15 min, the cyanotic areas of fingers 2 and 3 darkened, fingers 1 and 4 became cyanosed at their tips, capillary pulsation was just distinct over the whole palm, but in no finger tip, digital arterial pulses were felt at the bases of fingers 4 and 5, but not in fingers 1, 2 and 3.

The left hand showed the same joint deformity as the right. All the fingers of this hand were cold and cyanosed, and distinctly swollen. The

discoloration extended through the whole length of fingers 2, 3 and 4, and involved the tips of 1 and 5. The 2nd, 3rd and 4th fingers were all very tender, and the pulp of each presented considerable areas of necrosis. The left radial pulse was large, but no ulnar or digital pulse was palpable.

Three inches above the ankle was the large scar of a healed ulcer. The dorsalis pedis artery pulsated freely on both sides, the posterior tibial pulsation was felt on the left side only. On the right side, all the toes and the adjoining part of the foot were flushed and a little cyanosed. The ball of this foot was distinctly swollen, hot and extremely tender, but no part of the skin had necrosed.

The patient was suffering from general arterial disease and high blood tension (220 mm Hg). Her heart was enlarged and presented gallop rhythm. The fundi showed arteriosclerotic retinitis, the blood contained 117 mg urea per 100 cc, the urine was normal, the Wassermann reaction was negative. Ten days after being examined she died of cerebral hæmorrhage.

Autopsy. The heart weighed 185 gm, the whole aorta was in a state of advanced atheroma, extending into all the vessels of the head, neck and limbs, with ulceration in the aorta itself. The right kidney contained a few calculi and was almost completely atrophic. The left was small and granular, its vessels were patent but diseased.

On the right side the ulnar and radial arteries, the deep palmar arch and the four arteries to the index and middle fingers were dissected out. On the left side the digital vessels to the fifth finger only were examined. Pieces of artery, 1 cm long, were excised and sectioned serially, the sections being stained on separate slides with hæmatoxylin and eosin, Van Gieson's stain, or Weigert's elastic stain. Every vessel examined showed fibrosis of the media and slight or moderate general thickening of the intima. This thickening of intima was one throughout which coarse elastic fibres were found, from which we concluded its underlying process to have been arteriosclerotic. In addition to this general change in the arteries were more local changes which will be described for the vessels separately.

Left radial artery, taken three inches proximal to wrist joint. The lumen was patent but over a length of 2 mm was reduced to an eccentric chunk by great intimal thickening which was relatively cellular and contained little or no elastic tissue.

Left ulnar artery, taken three inches proximal to the wrist joint. Proximally and distally the lumen was closed by a heavily pigmented cannalising clot, in the intermediate portion of the vessel the lumen was open.

The left deep palmar arch. Where examined, near its origin from the radial, the lumen was patent.

The left common digital artery to the 4th and 5th fingers, where examined, in the proximal part of its course, the lumen was patent.

Arteries supplying left index finger. (a) *Arteria volaris indicis radialis* in the palm had an open lumen throughout the centimetre examined. At the base of the finger, the lumen was patent but greatly reduced, and at one point almost obliterated by intimal thickening, sparsely cellular and containing scattered fine elastic fibres. At the finger tip, a centimetre of the artery, just proximal to the necrotic area, was widely dilated and unthickened in its proximal parts. Traced distally a cap of recent blood clot was succeeded by an obliterating thrombus in an advanced stage of organisation. At the point of obstruction, the vessel wall was greatly contracted, and its adventitia surrounded by dense connective tissue, at this point the thrombus and all coats of the vessel contained much brown pigment. (b) Digital artery of ulnar side

At the base of the finger this artery was small, and the lumen much reduced by intimal thickening contained fresh blood throughout the piece examined. In the distal centimetre of the finger the vessel could not be distinguished with certainty, though the sections included all the soft tissues of this side of the digit cut transversely.

The digital arteries of the left middle finger At the base of the finger, the lumen of one of the digital vessels was completely obliterated by organising pigmented clot, the lumen of the other was open but reduced by intimal thickening. At the finger tip, just proximal to the necrotic area, both vessels were completely obstructed by organised, pigmented, canalised clot.

The digital arteries of the right little finger (a) Artery of radial side At the base of the finger, the lumen of the vessel was almost obliterated by intimal thickening containing little elastic tissue. Traced distally the lumen was closed first by fresh clot, then by hyaline clot and then by deeply pigmented organised thrombus. Near the tip of the finger the lumen was first open, and then closed by organised canalised and deeply pigmented thrombus. (b) Artery of ulnar side At the base of the finger the lumen was patent, except for a short stretch where it was occupied by hyaline thrombus beginning to organise. At the finger tip the lumen of the vessel was patent.

Comment A sufficient number of arterial specimens were examined and have been described to make it clear that the vessels of the hands were the seat of widespread disease. The vessels presented general arteriosclerosis and in addition their lumina were obliterated in many places by fresh or organising thrombi. Such thrombi were found in the vessels of all fingers examined, they were mostly in a state of relatively advanced organisation, and evidently more or less contemporaneous, here and there, however, additional thrombi had formed more recently. Thus thrombotic disease was found outside the area of actual necrosis, in the proximal as well as in the distal parts of the fingers, and even within and proximal to the hand, it was found not only in the fingers presenting necrosis at their tips but in a finger presenting only occasional discoloration. To correlate the occurrence of actual necrosis with particular degrees of arterial involvement in these hands would at least require information as to the condition of all the arteries in their whole length, and ability precisely to date the various lesions, it would further require knowledge of early pathological events within the actual area necrosed. This full information is not available and it is improbable, even if obtained, that it would carry us further. It is obvious that all the tissues not in a state of necrosis at the time of death were supplied by some blood, to estimate exactly the amount flowing to various parts of the fingers by histological means after death is beyond our power. The appearance and reactions of the fingers during life is the best guide to the state of their circulation at that time, our histological findings clearly justify us in concluding that the defect in circulation witnessed was in all fingers due to the same cause, namely, obstruction due to thrombi occurring in a number of vessels already the seat of senile arteriosclerosis.

Case 20 *Acute and permanent obstruction of many arteries in hand and fingers in an old woman, leading to gangrene, preceded for a few years by spasmodic closure of the vessels* *Autopsy*

M B, a woman of 73 years had enjoyed good health apart from occasional indigestion. Her diet had never been peculiar, she ate white bread usually and brown occasionally, but no rye bread. For 5 years she had noticed that the fingers of both hands became white to their bases and numb at their tips in cold weather. The attacks were at first infrequent but became more

frequent, though rarely occurring in the summer months. In January, 1932, the tip of the left 3rd finger became painful and shortly it turned "black." About the same time her other fingers became blue and painful, especially but not exclusively when cold. The skin of the affected fingers tended to scale, and slowly healing septic spots developed on the proximal interphalangeal joints. The condition remained unchanged until she was admitted to hospital on April the 1st, 1932, for a general erythema of the skin of the body, with swollen eyelids, the origin of this presumably toxic erythema remained obscure; it was accompanied by mild fever (101°F), both fever and rash subsided in a week and the skin desquamated. The blood pressure was 154 systolic and 100 diastolic.

On admission the tip of the 3rd finger of the left hand was seen to be gangrenous, to a line half way up the nail, this necrosed tissue was separated from the rest of the finger by a sharp line, from which pus exuded. There were small areas of depressed necrosed tissue opposite the proximal interphalangeal joints of this finger and the 2nd finger. The ends of fingers 3, 4 and 5 were cyanosed, so was finger 2 in its length. On the right hand similar small necrosed areas were seen on fingers 2 and 4. Cyanosis was present in the tip of finger 1, over the whole of fingers 2 and 5, and over the last two phalanges of fingers 3 and 4. The cyanosis of fingers 2 and 3 was full. All the fingers were warm, having been under the bedclothes. The radial and ulnar pulses were easily felt, digital pulses were felt opposite the proximal phalanx of fingers 2, 3 and 5 of the left hand but not in the right hand. Immersion of the right hand while in this state in water at 30° for 15 min failed to remove the cyanosis, which remained full in fingers 2 and 3 and deep in the remainder. Placed in water at 40° for another 12 min the cyanosis lessened but was still quite definite. Such stability of cyanosis is not found when closure of digital arteries is spasmodic. A similar distribution of cyanosis was seen in the hands on other days, the cyanosis extending also to the thenar and hypothenar eminence of the right hand. The skin of the fingers was normally mobile and unswollen, the fingers could be flexed fully.

The patient's trunk was enclosed in a warm chamber (63°) for 70 min, the tips of the chiefly affected fingers showed little or no rise of temperature, the fingers became pinker in colour but still remained cyanosed. On another occasion an optical capsule was used to test the extent of arterial pulsation in the 2nd left finger at various temperatures up to 45° . The pulsation was very greatly reduced below normality at all temperatures. These tests and the continued cyanosis provided clear evidence of structural disease in the arteries concerned.

Although the anterior tibial vessels could be traced by their pulsation to the middle of the metatarsal bones, the tips of all the toes were constantly cyanotic.

The condition of the hands and feet remained substantially unchanged during the patient's stay in hospital. On May the 4th she was again febrile,

the temperature rising to 104°F, an abscess developed on the left buttock, this was opened on the 5th May, but the temperature rose steeply a few days later and she died on the 13th

Autopsy A heart of normal size was found, exhibiting calcified aortic and mitral valves, general arteriosclerosis was present

The radial, ulnar, and palmar arteries, and the digital arteries of index and middle fingers of both hands were dissected out, and many portions excised and examined, in the manner described for the last case. The appearances were so similar to those seen in the last patient that it is unnecessary again to describe them in detail. All the vessels examined were diseased. The radial arteries were patent but presented patches of intimal thickening, containing sparse elastic tissue, and the medial coats were sclerosed. The ulnar arteries presented more advanced and recent disease, being largely obstructed by organised thrombi (recent and old) and by fresh blood clot. The palmar arches were likewise diseased, their lumina being reduced and in places almost obliterated by old standing thickening of the intima. The most advanced disease was found in the digital arteries themselves and especially in their distal parts. All of the five digital arteries examined presented conspicuous old standing intimal thickening and some medial sclerosis, four out of the five were found to be blocked in some part of the pieces examined by organised thrombus, dense, invaded by elastic fibres, and here and there canalised, though rarely pigmented, the fifth was reduced to a very narrow slit by conspicuous intimal thickening. Although the chief obstructing thrombi described were not recent, other thrombi of more recent origin were found from place to place, namely, fresh blood clot in one place, hyaline clot in another, more nucleated or more canalised pigmented tissue being found in yet another.

The appearances were consistent with thrombotic obstruction that had happened some months previously and had progressed by the addition of later thromboses. It was impossible to pick out and identify reductions of the lumina of the vessels, by tissue of such an age as to account for the attacks of transient cyanosis during the earlier years of her malady, unless these were to be accounted for by the general intimal thickening. Though it is possible that structural disease was responsible for those attacks, the case can hardly be used in evidence for or against this origin of the Raynaud's phenomenon, owing to the extent of later changes in the tissues of the vessels. But the case does illustrate, like that which precedes it, how a number of fingers can be brought to the verge of, or actually to the state of, necrosis by thrombosis at a number of distinct points in different vessels.

Massive gangrene in elderly people, whether it involves a single toe, the whole foot, or foot and leg, is recognised usually to result from senile disease in the main arteries, it is often associated with diabetes. Gangrene in the senile is almost always in the lower, and rarely in the upper, limbs.

Cases of bilateral gangrene of digits like those here described seem to be very rare, Hutchinson described an example in a man of 80 years, and Radziszewski in a diabetic of 57 years. Very little has been discovered about the cause of such gangrene in the senile. The examination of our own two patients shows that it can arise as a consequence of old standing disease in the arteries of the hand and fingers upon which clotting takes place and leads to abrupt and damaging occlusions. So much is certain, but the reason why fingers of both hands simultaneously become gangrenous, or to particularise, why clots should form almost simultaneously in different arteries remains undetermined. It may be that a nutritional change happens in the walls of the vessels concerned resulting in thrombosis. A case of

TABLE III
Bilateral gangrene of digits, single attacks in elderly cachectic or syphilitic subjects

Author	Sex and age	Gangrene in	Bilateral	Agency
Hutchinson (19)	M 80	fingers and toes	yes	Senile arterial disease
Radziszewski (38)	M 57	fingers	yes	Arterial disease alcohol diabetes
Pastur and Jones (33)	M 61	toe nose	yes	Cancer of stomach
Hamilton (15)	M 54	fingers	yes	Cancer of œsophagus
Bennet and Poulton (4)	M 60	fingers	yes	Cancer of stomach previous chilblains
Raynaud (39, Case 16)	M 34	fingers and toes	yes	Syphilitic subject
Morgan (30)	M 28	fingers and ears (blue nose)	yes	Syphilitic subject

* The authors have ascribed the gangrene to stimulation of the sympathetic a view however, which has been criticised adversely (23 p 87)

bilateral gangrene of the feet in a woman of 73 was described by Recklinghausen (10), he found no obstruction in the main arteries of leg or foot but described numerous hyaline thrombotic plugs in healthy small arteries and capillary loops of subcutaneous and deep cutis tissues, these he believed to have been responsible for the necrosis and likened them to similar plugs which he had found in necrosis of the cock's comb after ergot poisoning. It may be appropriate also to refer here to Dufour's report (9). His patient, is entered in Table II because her gangrene came during convalescence from pneumonia, but she was 58 years of age and for this reason might have been included in Table III. Dufour examined the vessels of her index finger but, though he found intimal proliferation, believed that obstruction was insufficient to account for gangrene. We think his examination failed to cover adequate lengths of artery.

Occasionally a similar clinical type of gangrene of digits occurs in the cachexia of advanced cancerous disease, although old standing arterial

disease may be concerned here too, the general state of these patients suggests defective nutrition of the vessels or tissues supplied as a factor Dr Grant has reminded us, pertinently, that these cases customarily show thrombi upon the heart valves These cases are referred to and are exemplified in Table III mainly to stimulate their further investigation and especially to urge an examination of the smaller arteries when opportunity occurs Two cases of similar digital gangrene in tertiary syphilitic subjects have been included in the table for the reason that, while here again nothing is known of the condition of the small arteries supplying the affected digits, they are also cases in which this investigation should be done

C RAYNAUD'S PHENOMENON AND GANGRENE IN CASES OF
ARTERIAL DISEASE

8 THROMBOANGELITIS OBLITERANS ASSOCIATED WITH RAYNAUD'S
PHENOMENON

*Case 21 Incomplete Raynaud phenomenon in a case of progressive
thromboangietis obliterans*

C M first came under observation in October, 1930, at the age of 38 In 1923 his right foot was amputated owing to gangrene of his great toe and loss of pulsation in the arteries of his foot A year later his left leg was amputated above the knee for gangrene of the foot which had become pulseless He remained well until the winter of 1927-8 when he noticed occasional blueness of the left 5th finger on cold days This disappeared with the advent of warmer weather, to reappear in the autumn of 1928, and shortly the 4th and a little later the 3rd finger on the same hand were affected similarly A small dry scab formed on the 3rd finger and became detached in February, 1929

The man was a gentle, he had eaten no bread but white, his urine occasionally contained a trace of sugar on ordinary diet His blood pressure was normal He was under observation for 4 years During this period the three affected fingers were seen to be cyanosed on a number of occasions in cold weather and after immersion in cold water, but they were never fully cyanosed and attempts to make them so by cooling them failed There was no history of actual blanching, or of numbness, to suggest that the circulation to these fingers was ever arrested for long periods of time

The radial pulses were equal, and these and the right ulnar pulse normal, but the left ulnar pulse could not be felt Obliteration of the radial pulses cut off all or almost all the blood supply to the left but not to the right hand The affected fingers were slightly thinner and more tapered and they were persistently colder, and cooled more quickly after warming, than the corresponding fingers of the right hand, heating the body gave delayed and imperfect warming of the affected fingers Both hands were soaked in water at 43° for 15 min to dilate the arteries, the three last fingers of the left hand remained dusky (tint IX or X) while the corresponding fingers of the right hand were pink (tint VII or VIII), on the right the tips of the fingers showed capillary pulsation, on the left pulsation was doubtful or absent,

pulsation of the digital vessels was palpable at the base of each finger of the right hand, but only in the 1st finger of the left hand. Measurement of the digital pulsation by optical capsule in the warm hands, showed a conspicuously smaller pulse in the 3rd left than in the 3rd right finger. When after warming the hands the circulation to the two arms was arrested for 5 min and released, reactive hyperæmia was long delayed in the 3rd, 4th and 5th fingers of the left hand. Calorimetry at 30° showed the bloodflow to the right hand to be half as much again as that to the left hand. These observations and tests were all consistent and showed diminished bloodflow through the inner fingers of the left hand and evidence of obstructive disease in the arteries supplying them. The level of this obstructive disease must be placed as high as the ulnar artery, though that would not by itself suffice to explain the defective circulation, the tests, however, do not decide whether the additional defect was in the digital vessels themselves or in palmar arteries. In 1932, the tests described being then completed, the patient began to complain of coldness of the fingers 3, 4 and 5 on the right hand, and a small patch of gangrene appeared on the 4th finger. The right ulnar pulse had disappeared and the behaviour of the right and left fingers was now very similar, indicating defective circulation on both sides.

This case is used as an illustration of transient discoloration of the fingers in response to cold in a patient suffering from progressive thromboangiitis obliterans. It shows again how chronic structural vascular disease can give rise to symptoms of an intermittent character. In this instance, however, actual arrest of bloodflow did not occur, and it is unnecessary to suppose that the vessels were unduly sensitive to cold.

9 CERVICAL RIB OR CRUTON PRESSURE CAUSING RAYNAUD'S PHENOMENON OR GANGRENE

Case 22 Raynaud's phenomenon in one hand due to local arterial disease, the result of cervical rib

W P was a laundry man of 24 years. His work consisted in managing a washing machine. He came complaining that for six months, since the advent of cold weather, he had noticed the 2nd, 3rd and 4th fingers of his left hand become white and numb, first while bathing and later one or more times each day at his work. He was sure that this discoloration was of recent origin, his hand being quite normal previously, and his right hand being unaffected. Warming the fingers, when they were discoloured, would quickly restore them. He had experienced no pain in his arm. His feet were normal.

The hands were strongly built, the fingers could be flexed fully, and their skin was normally mobile. The radial and ulnar pulses were equal on the two sides and normal with the hands down, but if the arms were raised to the level of the shoulder the pulse disappeared in the left arm from the clavicle downwards, but continued on the right side. There was no muscular wasting. Movements of the hands were equally powerful, sensation in them

was normal. No abnormality was found, apart from roughening of skin and nails of both hands due to his heavy manual work, until they were placed in water at 15°, in 8 min all the fingers of the left hand, and especially fingers 2, 3 and 4 were cyanosed. The hands were immersed in water at 36° for 15 min, during the last 5 of which the circulation to both arms was arrested. On release, the flush of reactive hyperæmia promptly invaded the whole of both hands, with the exception of the tips of the left 2nd and 3rd fingers in which it was delayed for a few seconds. The hands were immersed in water at 40° and 45° and the pulsation of the vessels in the two 2nd fingers compared by means of an optical capsule. The pulsation of the left finger was scarcely more than half that of the right at these temperatures, a later test at 40° showed definite reduction of pulsation in fingers 2, 3, 4 and 5 of the left as compared with the right hand. On examining the fingers, after their immersion in hot water, capillary pulsation was very clear in all the right finger tips and in the palm of this hand, it was equally clear in the left palm but was found only in the tip of the 5th finger of this hand. When warm the palmar arteries could be felt pulsating equally in the two hands. When the patient's body was enclosed in the warm chamber, the hands being cool and remaining exposed, the rise of temperature was much delayed in the 2nd, 3rd and 4th left fingers, and failed to reach the full value (30.6° instead of 32.6° as in the control fingers). Thus all these tests were consistent in pointing to a structural defect in the vessels of the fingers of the left hand, emphasising as chiefly affected fingers 2, 3 and 4, the fingers of which the patient originally complained.

Operation An X-ray photograph showed bilateral cervical ribs, the left one was exposed and dealt with by Mr Wilfred Trotter on January the 24th. The cervical rib was well developed, ending in a large boss which articulated with the first rib. The subclavian artery passed over this boss, behind the boss lay the cords of the brachial plexus, the lowest cord being in relation with the cervical rib but under no tension. The artery passed in the groove between scalenus anticus and rib, the posterior edge of this muscle indented the artery and pressed it backwards. After leaving the groove, in which the artery was of normal size, it dilated to form a fusiform aneurism of about twice normal diameter, lying on the cervical and first rib. The arterial pulsation tended to become less obvious as the swelling was reached, abduction of the arm to a right angle obliterated the pulse, the artery being seen to be obstructed between the clavicle and the boss of the cervical rib. The anterior half of the rib, together with the boss of articulation, were excised, the posterior half of the rib was left, as Mr Trotter felt satisfied that the plexus was under no tension. After this partial removal of the rib the arm could be lifted above the level of the shoulder without affecting the pulse. The expanded subclavian artery was covered with and bound to the underlying rib by very dense fibrous tissue, apparently the result of chronic inflammation, arising out of the trauma of compression between rib and clavicle.

Course Seen on May the 29th and October the 4th, 1934, 4 and 8 months after operation, the patient stated that the attacks of blueness of the left fingers had almost ceased to occur, he experienced them only on occasions as when swimming in cold water. In May, immersion of the hands at 15° for 20 min rendered all the left, but not the right fingers, cyanotic, in October cyanosis appeared in the left index finger only under the same test. Immersion at 15° produced vivid capillary pulsation in all the right and slight pulsation in all the left finger tips, at both examinations.

Until recently, the vascular symptoms arising in cases of cervical rib have been attributed to obstruction of the subclavian artery as it passes over the cervical rib. In 1912, Todd (47), became dissatisfied with the views then current, he emphasised the cord-like thickening of the vessels in the length of the arm in a case of cervical rib with vascular symptoms, and in a later investigation found the walls of the vessels greatly thickened and filled with organised bloodclot. This cord-like (thrombotic) condition of the arteries in the length of the limb has also been described by others (Gordon (14), Keen (20), Telford (15, Case 2) and Benedek (3)). Todd like Gordon, suggested that these changes in the vessels arise from interference with certain sympathetic nerve fibres. The fibres, which Todd suspected, join the lower cord of the brachial plexus by passing along the 1st dorsal nerve from the sympathetic chain and these were supposed from their position to be liable to mechanical pressure from the uppermost rib. Todd believed these sympathetic fibres to be paralysed and that great thickening of the wall of the main vessel might be a resultant tropic change. Telford and Stopford (46), while agreeing with the idea that these special sympathetic fibres are pressed upon, modified and elaborated previous views. They suggested that the nerve fibres are irritated by pressure, thus causing spasm of the arteries of the arm. This spasm of arteries is thought to induce constriction or even obliteration of the vaso-vasorum in their walls and thus to cause nutritional changes leading to thrombosis upon the corresponding arterial walls. It seems to us that this idea of pressure on a special group of sympathetic fibres is too speculative to be acceptable. Moreover it is open to a number of objections. It would be necessary to assume that sympathetic fibres passing to all the main arteries of the arm, and to the arteries of the fingers, are incorporated in the 1st dorsal nerve and pass through it to the plexus, an assumption which scarcely seems permissible. If pressure on the vasomotor nerves leads as Todd thought to paralysis, it should cause vasodilatation in the corresponding territory. The reverse process, namely, continued irritation of a peripheral nerve by pressure, in which Telford and Stopford believe, is an idea we find difficulty in accepting on general grounds, and on the particular ground that any spasm so induced might be expected to be intermittent in the early stage and give way to paralysis later. In these cases of cervical rib there is no evidence of a preliminary or late stage of vasodilatation, and there is none of

spasmodic closure of the arteries in response to a supposed stimulation of the brachial nerves

Telford and Stopford sum up the position by saying “We are at once faced with the problem of why in one case of cervical rib the symptoms may be purely sensory and motor, whilst in another the results are predominantly thrombotic” They believe that arrangement of the sympathetic fibres in the plexus accounts for the difference, the fibres being supposed to pass along the lower cord as an exposed strand in the cases presenting vascular manifestations and mixed with the rest of the fibres of this cord in others, this is the suggestion, but there is no evidence that the anatomical arrangement has this difference in the two clinical types of case. It seems improbable too, that pressure could be exerted upon the lower cord of the plexus for long periods of time, and adequately to irritate or paralyse the sympathetic fibres without affecting the sensory and motor nerve of the same cord, for sharp differentiation of this kind is necessary to the explanation considered. The general tenor of the summing up, is acceptable, though we would express the matter a little differently, in saying that it is to be ascertained why cases of cervical rib fall into two main groups, why in one the symptoms are purely those of peripheral nerve injury, and why in the other they are purely those accountable for by ischæmia. The correct reply is almost certainly that in one case there is local interference with the brachial plexus and in the other with the subclavian artery. In separating plexus symptoms from those of arterial origin, it is important to realise that many of the nervous symptoms exhibited by cases of cervical rib are primarily vascular and not derived from pressure on nerves. Embolism of an artery is often followed by much pain, ischæmia renders a muscle painful in its work and enfeebles it. Numbness is a frequent symptom of ischæmia of the skin, and tingling a common sequel to temporary loss of blood supply. Tissues threatened by gangrene are often extremely tender and painful. Thus, tenderness, pain, tingling, sensory loss, and motor weakness may each and all be explained from time to time without invoking damage to the brachial plexus. Loss of sensory and motor function recognisable as derived from continued pressure on the lower cord of the brachial plexus fall into the usual patterns of plexus injuries, the paralysing and wasting of specific muscles and anaesthesia in definite areas of skin, and these are disturbances which can rarely be expected to show recovery, after relief of compression by surgical interference, until the nerves involved have regenerated. It is important also to recognise that simple disuse, with or without paralysis, will induce continued coldness with some cyanotic discoloration of the limb, and consequently that such symptoms cannot be accepted as signs either of vascular thrombosis or of vascular spasm. Reading past case records it is evident that confusion has often arisen in the interpretation of symptoms because these facts have not been recognised and, recognising and allowing for them, it becomes clear that the cases fall much more clearly into nervous and vascular types than has hitherto been realised.

But we agree that the full display of vascular symptoms cannot arise directly out of compression or out of obstruction of the subclavian artery by local thrombosis. The hypothesis of sympathetic stimulation, however, is too difficult in its application to be acceptable. As an alternative we suggest the hypothesis of local thrombosis and resultant embolism. In our own patient and in others displaying vascular symptoms and described previously (Poland (34), Keen (20), Leriche (22)) there has been evidence of local damage to the artery, the vessel is dilated, aneurysmal, or buried in recent or old inflammatory tissue. Billington (5), in a case presenting vascular symptoms, excised an aneurysmal subclavian artery, he found the lumen almost full of clot and the arterial wall presenting signs of trauma. In Baum's case (1) the disturbances were ultimately cured by clotting within a subclavian artery described as aneurysmal. In our own case the injury is ascribed to ascertained compression of the artery by the clavicle, and similar intermittent compression is probable in other patients, for postural disappearance of the pulse is very frequent in cases of cervical rib (Quervain (37), Murphy (31), Keen (20), Sargent (42), and personal observations). We suggest that as a result of traumatic injury, as through compression by the clavicle, the wall of the subclavian artery becomes the seat of thrombi, though the vessel usually remains pervious, repeated movement detaches clots and the resultant embolism accounts for the chief vascular phenomena observed. Thus, a large embolus plugging the bifurcation of the brachial artery may give rise to sudden severe pain and will reduce the limb to an algid, cyanosed state as in Newell's case (32), a state from which recovery is slow and imperfect. Many small emboli lodging in the digital and palmar arteries would gradually block these vessels and produce in the fingers the picture of diseased digital vessels and their spasmodic closure in response to cold, which our own patient and those of Leriche (22), Benedek (3), and probably that of Gordon (14), displayed, and this action of cold is to be regarded as a purely local action which, by increasing directly the tone in the vessels affected, obliterates their lumina, already decreased by disease. Intermediate emboli lodging in radial and ulnar artery would bring the threat of gangrene to given fingers. And since the radial artery is the larger and more vital of the two main vessels supplying the hand, it will receive more emboli than the ulnar and produce the more conspicuous effects, the well recognised but obscure predominance of gangrene in the index finger in these cases, may be due to this cause. Embolism, followed by further emboli, and by thrombus formation above and below the first embolic clot, will lead to the obliteration of lumen that is known to occur in the arteries in these cases, it will explain why a disturbance involves the distal vessels first and proximal vessels later, as is strongly suggested by reviewing together such cases as those of Baum (1), Ehrlich (10), Gordon (14), Keen (20), Leriche (22), Telford (45, Case 2), Benedek (3), and ourselves, such cases indicate early disease of digital vessels, or early involvement of fingers with later involvement of hand and arm, or loss of a distal radial pulse and later of more

proximal pulses in the arm Recovery of the limb often follows removal of the cervical rib This recovery may begin within a few days or may be prolonged, pulsation of the arteries at the wrist may reappear ultimately or it may not It is recognised that such recovery is due to the opening up of collateral channels, sometimes observed clinically The opening of a collateral circulation after obstruction of the main artery should occur whether rib is removed or not, this actually happens (*see* Hodgson (18, case 38)), but collateral channels will tend to remain effective or to become increasingly effective only if embolism ceases to occur In our view vascular recovery is due to cessation of intermittent compression of the subclavian artery, which by damage causes the formation and detachment of clots, and in addition interferes with the nutrition of the vessels lower down by robbing them temporarily of blood supply

Case 23 Raynaud phenomenon in one hand, due to local arterial disease, and probably resulting from compression of the axillary artery by a crutch

W K, was a printer (relief stamper) When 7 years old, his right leg was amputated at the hip in consequence of disease following injury At 8 years his left knee became diseased and the joint was excised From 8 years onwards he used crutches, for 50 years while working or at home he used the left crutch only, he used two only when walking in the street, his weight then falling mainly on the left crutch From 58 years he used two crutches always He had never experienced any paralysis in his arms, but numbness occasionally developed in the tips of the left fingers after long walking, this numbness would disappear rapidly, being replaced by transient "pins and needles" on dropping the crutch He remained healthy until the winter of 1928-29, when, at the age of 62, he noticed that the 2nd and 3rd fingers of his left hand became blue and painful on exposure out of doors on cold days Little crusts formed around the nails of these fingers, but no open sore In the following summer the hand seemed almost normal During the winter of 1929-30 his trouble returned, the fingers became so painful that he was obliged to stop working, and the 1st and 4th fingers also became involved, crusts again formed on fingers 2 and 3 The right hand remained quite normal His face was unaffected His urine had never shown blood

He came under our observation in mid-summer 1930 At this time his fingers, which had been slowly recovering from necrosis, were almost healed The 2nd, 3rd and 4th fingers were shortened, their ends were scarred, the pulp of each being much reduced and the nails distorted The nail and necrosed nail-bed of finger 4 were still separating The pulp of the 5th finger was very reduced and the finger tapered, but no necrosis had occurred in this finger Movement at the interphalangeal joints of all these fingers was limited When he came into the room (temp 17.5°) all the fingers were of good colour, but fingers 2 to 5 quickly became fully cyanotic (tint XV) in their length The discoloration also affected the tip of the thumb on its palmar surface, and the back of the hand to a lesser extent The left was weaker than the right radial pulse, of the ulnar pulses only the right was

palpable The fingers of the right hand were all warm, those of the left hand were all cold, the 2nd, 3rd and 4th being just above room temperature, and the 1st and 5th fingers being a little warmer The coldness and cyanosis of the affected fingers was repeatedly and constantly observed in cool or cold atmospheres When the hands were immersed in water at 35° for 10 minutes the fingers were almost alike in colour When immersed at 15° the fingers of the left hand rapidly became fully cyanosed indicating complete stoppage of bloodflow through them If the hands were warmed (at 35°) and the circulation through both arms arrested for 5 min and released, the right hand flushed red in all parts within a few seconds, but in the left hand it was delayed, starting at the wrist at 10 sec, reaching the bases of the fingers in 25 sec, and being delayed at the ends of the fingers for as much as 1 or 2 min After soaking the hands in water at 43° for

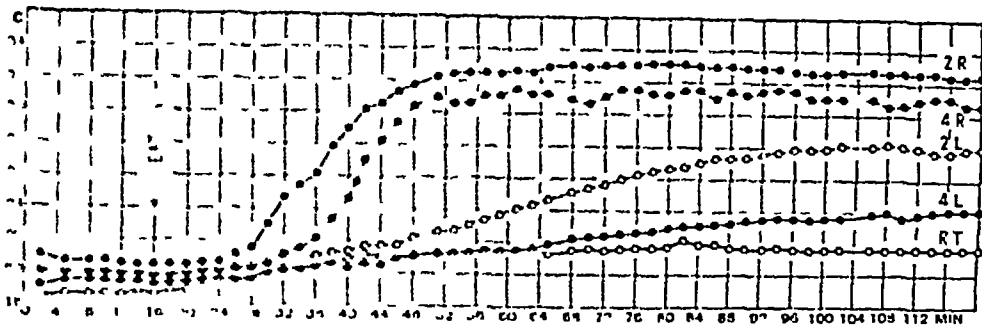


Fig 5 Case 23 July the 24th, 1930 Temperature of the 2nd and 4th fingers of the right (unaffected) and left (affected) hand The observations were made in a cool room (RT — room temperature) The chart shows the effect of heating the body in a warm chamber Vasodilatation occurs quickly and fully in the right fingers, but the bloodflow increases slowly and imperfectly in the left fingers

10 min, the chiefly affected fingers were a little more cyanotic than the control fingers, capillary pulsation was present in all the finger tips of the right but in none of those of the left hand, pulsation of the digital arteries was palpable on the right but not on the left side and, measured by optical capsule, was reduced on the left to but a small fraction of its extent on the right side At this temperature the left radial pulse was large but the left ulnar pulse remained imperceptible, if this warmed hand was held aloft, the radial pulse obliterated, and the hand lowered, the palm flushed only when the radial pulse was released, and not, as in the case of the right hand as soon as it was lowered Immersion of the hands in calorimeters at 30° , in a room at 21° , showed heat to be lost from the right nearly thrice as fast as from the left hand Heating the body in the warm chamber quickly determined a rise of temperature in the right fingers, but the rise in the left fingers was far more gradual and less extensive (Fig 5) Similarly, anaesthetisation of the left ulnar nerve led to an incomplete rise of temperature in the 5th finger (to 27° at room temp of 19°).

The results of these tests were all consistent, they showed greatly diminished flow of blood to the fingers of the left hand and to fingers 2, 3 and 4 particularly. They indicated that the vessels concerned were the seat of obstructive disease. Six months after these tests were made the radial pulse also disappeared from the left wrist. According to the history, the first event in the hand was obstruction of branches of the radial artery, causing deficient circulation to fingers 2 and 3. This may have resulted from obliteration of the corresponding digital arteries or of the palmar arch from which they spring. Later came obliteration of the ulnar artery and of arteries supplying the thumb, and then obliteration of the radial vessel, thus the affection of the vessels of the hand was at this time extensive (January, 1931). From the occasion when he was first seen pulsation in the left brachial artery seemed slightly but just distinctly less than in the right vessel, and the Pachon oscilometer showed a slightly reduced excursion when applied to both upper arm and forearm on the left side.

In June, 1934, in his 67th year, his hand was in much the same state, though he thought the attacks of discoloration a little less frequent, he had walked little for a year. On examination the left hand was found unchanged, but there was further change in the arteries supplying the arm. The pulsations of the left subclavian artery and upper parts of the axillary artery were equal to those on the right side. Distally arterial pulsation was visible and palpable on the right side along the whole length of the upper arm, it was visible on the left side only to the end of the axillary artery, decreasing rather abruptly in the region of the 3rd part of this vessel. On the left side the artery in its 3rd axillary and 1st brachial portions was felt as a hard cord pulsating feebly in contrast to the vigorous pulse in the corresponding parts of the right artery, it also differed from the latter in being smaller in size and far less compressible. The pulsation and the oscillemetric excursion of the remainder of the left brachial artery were greatly diminished and were absent below the junction of the middle and lower thirds of the upper arm. The pulses were normal throughout the right arm. The mark of the crutch was manifest in the axillæ of both sides. The area of pressure was mapped out by increased vascularity and deep pigmentation of the skin, over a sharply defined area about 10 or 11 cm wide passing right through the axilla from back to front. This area of chronically marked skin also presented on both sides a series of numerous scattered papillomata, these were larger and more numerous on the left side. On its inner side, the area of discoloured skin began about the level of the junction of 2nd and 3rd part of the axillary artery, where on the left side arterial pulsation abruptly diminished, in its breadth it covered with more or less close correspondence the stretch of the left artery that was felt as a hard cord.

When standing ordinarily upon his crutches, his pulse (right or left) disappeared or became very weak below the crutch, as soon as the weight was thrown upon it. After standing several minutes with his weight on the

left, the weight was thrown onto the right crutch, and reactive hyperæmia then appeared in the left hand

Now the heart of this man was unenlarged and there was no more sign of arterial disease in the right brachial artery than is usual in a man of his years. In the lower limb arterial pulsation was normal even in the foot. The blood pressures were 150 systolic and 90 diastolic, his urine was normal, his retinal vessels appeared normal. The case was manifestly one of gross disease picking out the arteries of the left arm. It seems clear that this disease arose primarily out of long continued compression of the left axillary artery, giving rise ultimately to gross local thickening of the vessel and to secondary changes in its tributaries. The case is included in the present series primarily to illustrate the occurrence of Raynaud's phenomenon in fingers, the arteries supplying which were the seat of disease. It is placed next in the series to the case of cervical rib because it presents obvious resemblances to the latter and because it is difficult to arrive at any other conclusion than that the two examples of arterial disease arose similarly, and, as we think by intermittent compression and traumatic injury of the main artery of the limb. For it is hardly to be believed that pressure upon nerves in the subclavian region and in the lower axillary region could select for similar and long-continued irritation the same series of vasoconstrictor nerves, producing through this irritation a nutritional change in the arteries of the arm. Direct evidence of nerve compression did not exist in either case, evidence of local compression and of damage to the artery was found in both, and the peripheral phenomena in both cases are adequately explained if we suppose the distal arterial changes to have resulted through emboli repeatedly formed and detached at the original seat of damage, and from nutritional disturbances directly arising out of long continued intermittent occlusion of the main vessel of the limb

GENERAL COMMENT

If all instances of temporary arrest of the circulation to the finger, or to other part of the body that is particularly prone to become cold, and all instances of symmetrical gangrene of digits without demonstrable obstruction to the main arteries of the limb, are still to be classed as instances of "Raynaud's disease," then a number of quite distinct conditions will continue to be grouped together. Such grouping cannot fail to obstruct enquiry into the causation of the various maladies, and to prevent proper appreciation of their natural history. One main object of this paper will have been realised if it has been made clear that many distinct maladies are being confused together, and if it is recognised that their separation is quite essential to the progress of future studies. We think that the term "Raynaud's disease" should be abandoned, it has already been responsible for much looseness of thought and writing. It is desirable that two phenomena should be considered separately, namely, what we may call "Raynaud's phenomenon," and gangrene or necrosis. The term "Raynaud's phenomenon" is used to

signify active and intermittent closure of small arteries of the order of those supplying the digits, a closure manifesting itself clinically in a pallid or fully cyanotic state of the affected skin. But even this phenomenon is not to be regarded as the result of one set of circumstances. It can be a purely spasmodic affair, but it can come also where there is obstructive disease in the digital arteries themselves or in vessels proximal to these, this structural disease being ultimately responsible for the whole circulatory abnormality. In fingers or other parts, the arterial supply to which has already been the seat of thrombotic or embolic processes, anastomotic sources of supply may fail to become established fully, and subsequently normal increases of tone, such as are induced by cold, will cause transient arrest or conspicuous reduction of bloodflow. Thus the original disturbance may be a sudden and non-recurring event, leaving behind it a proneness to attacks of cyanosis, which wrongly come to be regarded as signifying active disease. In studies of the maladies discussed, the events in each case must be regarded upon their individual merits, and abnormal vasomotor influences should not be invoked in explanation because it has become the traditional and convenient line of reasoning for the whole group, but only when there is clear supporting evidence of such causation.

A second main object of this paper is to suggest that it is a mistake ever to regard gangrene as the result of an uncomplicated spasmodic affection. When the circulation to the skin is shut off, there comes into immediate action a mechanism producing vasodilatation and manifesting itself ultimately in "reactive hyperæmia." It is known that constriction of the vessels, produced through sympathetic channels, will counteract this dilator mechanism in the early stages of its establishment, but as ischæmia is continued the vasodilator factor will become increasingly intense, and sooner or later the nerves themselves will become functionless locally. Thus it would seem inevitable on *a priori* grounds that a nervous vasoconstriction cannot be maintained sufficiently long to kill the skin. There is increasing evidence in the group of cases as a whole that when gangrene occurs, a structural change such as thrombosis has happened and permanently plugs the vessel. This is not the place to pursue this question further, the part played by intimal thickening and thrombi, not only in the large arteries, but also in those of the smaller size of the digital arteries, has been alluded to already in several places in the body of this paper. The view that thrombosis is an important factor must rest ultimately upon microscopic demonstration, and microscopic examination of the tissues concerned has not yet been carried nearly far enough. We refrain from discussing again (see 26) the very important question whether or not spasm can determine intimal or thrombotic changes within small arteries, and thus lead indirectly to permanent obstruction and necrosis. These are questions for future study. Meanwhile, and largely to provoke such study, we definitely suggest that intimal changes including thrombosis are usually or always responsible for the obliteration of small arteries leading to necrosis, and we have in

mind, not only the isolated attacks of discoloration and necrosis such as are seen in the bilateral digital gangrene described cases of in Group 5, but also the minute necrotic foci which form on the fingers of cases that are primarily spasmodic (Group 2)

SUMMARY

In the present article the following conditions are separately considered and when necessary exemplified

- 1 Intermittent spasm of digital arteries, without complication
This condition is shown often to be familial
- 2 Intermittent spasm of digital arteries with local nutritional changes

Reasons are given why intermittent spasm, whether associated with nutritional changes or not, should be attributed to a local fault of the vessels concerned

- 3 Intermittent spasm of digital arteries with generalised scleroderma
- 4 Raynaud's phenomenon arising out of local injury, including the use of vibrating tools
- 5 Bilateral gangrene of digits in the young, and with infection, this condition is regarded as probably the result of thrombotic closure of vessels
- 6 Bilateral gangrene with hæmoglobinuria from cold, a condition having probably a unique pathogeny
- 7 Bilateral gangrene of digits in the elderly, in which closure is shown to be thrombotic but preceded by disease of the small arteries
- 8 Thromboangitis obliterans associated with Raynaud's phenomenon
- 9 Cervical rib or crutch pressure causing Raynaud's phenomenon or gangrene, so it is thought, by thrombotic and embolic processes

A main purpose is to show that a number of distinct conditions has been described under the term "Raynaud's disease," separately to explore these, and to indicate directions in which new enquiries may be conducted. It is considered that the term "Raynaud's disease" should be abandoned

The present enquiries again point to the existence of a local fault as the cause both of Raynaud's phenomenon and of bilateral gangrene

It is suggested that gangrene is never the result of uncomplicated spasm of arteries. Evidence tends increasingly to show that gangrene depends upon structural occlusion of the vessels.

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OBSERVATIONS ON THE RATE OF WATER-LOSS BY MAN AT REST

PART I—DESCRIPTION OF A CONSTANT TEMPERATURE AND HUMIDITY ROOM

PART II—"SPONTANEOUS" DIURESIS DURING PROLONGED REST

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Introduction

WHEN under ordinary laboratory conditions the diuresis following water-ingestion by man is delayed by post-pituitary extract injected subcutaneously at the same time as, or before, the giving of the water, the renal response is smaller than the undelayed response. Experiments made under such conditions with the object of determining the immediate and ultimate fate of the observed deficit, soon showed the need for rigid control of environmental conditions as well as for accurate knowledge of the course of total water-loss. After obtaining this control we proceeded to investigate the effect of increasing degrees of water deficit, produced by long periods of rest, on the response of the kidneys to water-ingestion, and were confronted at the outset with an interfering phenomenon, namely a "spontaneous" diuresis which set in some time after the subject had lain down to rest.

In this paper we propose, first, to describe the room which has been constructed for the purpose of investigating such problems as those to which we have referred, and second, to record experiments undertaken with a view to gaining information on the characteristics of the "spontaneous" diuresis mentioned above, and to arriving eventually at its cause.

PART I—DESCRIPTION OF A CONSTANT TEMPERATURE AND HUMIDITY ROOM

That changes in temperature, humidity or rate of movement of the surrounding air have a profound effect on the rate of water loss by the human skin, is clear from the observations of Reinhard (24), Erismann (8) and Schuerbeck (28), observations which have been extended by Rubner and

Lewaschew (27) to the inclusion of the pulmonary water-loss, and so to the demonstration of a direct proportionality between relative humidity and the rate of loss of aqueous vapour by man over a certain range of air-temperature. The figures given by Rubner and Lewaschew (27) show that a change of air-temperature from 20° to 25° is accompanied by a rise in the rate of loss of aqueous vapour, by a lightly clothed person, of 10 and 20 g per hr at relative humidities of 80% and 6% respectively. At constant air-temperature of 25.1° the same authors found a rise in humidity from 30 to 80% to be accompanied by a fall in the vapourization-loss of 50 g per hr. More recently Whitehouse, Hancock and Haldane (35) have shown that immersion in baths of water or isotonic salt solution leads to a fall of about 30 g per hr in the rate of loss of water by the skin. That changes of such magnitude in the rate of vapourization-loss are reflected in inverse changes in the rate of urine flow is suggested by observations recorded in the two papers to which we have just referred. This being so, we might infer with reason from the figures given above, that changes in urine-flow ascribable directly to such variations in vapourization-loss as accompany the changes in air-temperature and humidity occurring during the course of a working day, would be small. The need for repetitive observations, however, together with the possibility that small variations in the conditions of the external environment would lead to changes in rate of urine flow by some means less direct than simple variation in rate of vapourization-loss, made a high degree of control of these conditions desirable if not imperative.

We required, then, for the investigation of our immediate and remoter problems, a room in which the ventilation, air temperature and humidity were under independent control, and in which the weight of the human subject could be followed with accuracy.

The many respiratory chambers designed for measurement of the gaseous and aqueous exchanges of man (1, 2, 4, 9, 11, 12, 16, 20, 26, 29) were considered unsuitable for our work for one or both of the following reasons. First, the smallness of their size imposed restriction in application and, in some cases, difficulty in ensuring uniformity in the atmospheric conditions throughout the chamber. Second, the lack of adequate provision for varying and maintaining these conditions, in detracting from the assurance of control, added difficulty to quantitative interpretation. We shall now proceed to give, first, the standard conditions of ventilation, of air-temperature and of humidity which we have chosen, with reasons for their choice, second, the means adopted to secure the maintenance of these conditions, and third, the arrangements selected for measuring changes in body-weight.

(a) Standard conditions of ventilation

We assume that under normal conditions of observation there will be a CO_2 production in the room of not more than 1400 c.c. per min at 0°C and 760 mm. Hg. This figure is taken from data by Haldane (10, p. 29), and

represents the CO_2 production of three men, one being at rest in bed and two walking at 2 miles per hour. At 26° , the standard condition of air-temperature chosen by us, this figure becomes 1530 c.c. and will raise the content in CO_2 of 3 cubic metres of air by 0.05%. The room should be ventilated, therefore, at an exchange of not less than 3 cubic metres per min. if the CO_2 content of the air within is to be held below 0.1% (see Table I). Further, provision must be made for large increases in this exchange should occasion require them.

(b) Standard conditions of air temperature and humidity

The dry- and wet-bulb air temperatures which we have chosen as standard for our investigations are 26° and 17.7° respectively.*

The former was found, at the chosen degree of humidity, to permit the subject of experiment to lie naked in the room without experiencing a sensation of cold on the one hand, or perspiration on the other (see Schierbeck (28), Rubner and Lewaschew (27), & Willebrand (36)). The latter temperature was adopted from the following considerations. In order that during a year's working hours the necessity of adding water vapour to the room-air might be approximately matched with that of removing it in the maintenance of constant dry- and wet-bulb temperatures, it seemed to us desirable that the wet-bulb temperature should be so chosen as to correspond with the mean absolute humidity for the hours 9 a.m. to 6 p.m. throughout the year. To this end the British Meteorological and Magnetic Year Book (31) was consulted. From the tables therein, giving the hourly values of temperature normals for the years 1871 to 1915 the mean temperature throughout the years, from 9 a.m. to 6 p.m., was derived. This was found to be 11.63° . Similarly, the tables of hourly values of normals in relative humidity for the 30 years 1886 to 1915 were consulted, and the average throughout the years from 9 a.m. to 6 p.m. was found to be 71.7%. The corresponding dew point would be 6.4° . The relative humidity figures had been derived from dry- and wet-bulb readings by means of Glaisher's factors (13). From these factors we find that the wet-bulb temperature corresponding with a dew point 6.4° and with a dry-bulb temperature of 26° is 14.6° . The aqueous vapour pressure of such air is 7.4 mm Hg (13). The practical difficulties, however, of maintaining within the room a vapour pressure of this value are very much greater when the outside air is warm and moist than when cold and dry, and it was because of these difficulties that we decided to maintain as one of our standard conditions an aqueous vapour pressure, as derived above, 40% greater than the mean value to which we have referred. This pressure, namely 10.4 mm Hg, corresponds with a dew point of 11.8° , and the dry-bulb temperature being 26° , the wet-bulb temperature, from Glaisher's factors, becomes 17.7° . Such air will contain 10.4 g. of water vapour per cubic metre (13). The aqueous vapour pressure of this air happens to be equal to the mean of the hourly values at Richmond, as calculated with the aid of Glaisher's factors, from 9 a.m. to 6 p.m. during the month of July for the years 1886-1915 when the mean of the hourly values of dry-bulb temperature over the same periods of time was 19.5° , i.e., considerably below that chosen as our standard value.

If we employ the August Apjohn formula (13), relating the difference between the dry- and wet-bulb temperatures to that between the saturated vapour pressure of water at the temperature of the wet-bulb and the actual pressure of water vapour in the air, giving the constant A the value for moving air as in a ventilated psychrometer, we find that the aqueous vapour pressure at dry- and wet-bulb temperatures of 26° and 17.7° respectively becomes 10.9 mm Hg, a figure in close agreement with that 10.4 mm Hg derived above by means of Glaisher's factors. But in order that we should know how nearly these derived figures approached the corresponding real value of the aqueous vapour pressure, and that we might have available an easy means for frequent tests of this correspondence, we have made and calibrated a chemical hygrometer as described by Rideal and Hannah (25). Two or three minutes only are required for making a determination of the aqueous vapour pressure by this method, and Rideal and Hannah give figures which show a variation of 2% only from those found gravimetrically. Readings obtained by means of this chemical hygrometer show that the aqueous vapour pressure of the room-air under our standard conditions is 9.6 mm Hg, i.e., 10% less than the mean of the two derived values given above. The relative humidity is 38%.

Our aim, then, has been so to devise means of warming or cooling, drying or moistening the air with which the room is ventilated as to maintain our

* The wet-bulb was ventilated in the small chamber designed for controlling the degree of humidity of the room air (see p. 376).

standard conditions of temperature and humidity within, independent of changing conditions of temperature and humidity without the room. The maintenance of these standard conditions must be automatically controlled through the course of an experiment. Further, the setting of the automatic control must be alterable at will, within wide limits, in order that the effects of a known change in temperature or humidity may be determined.

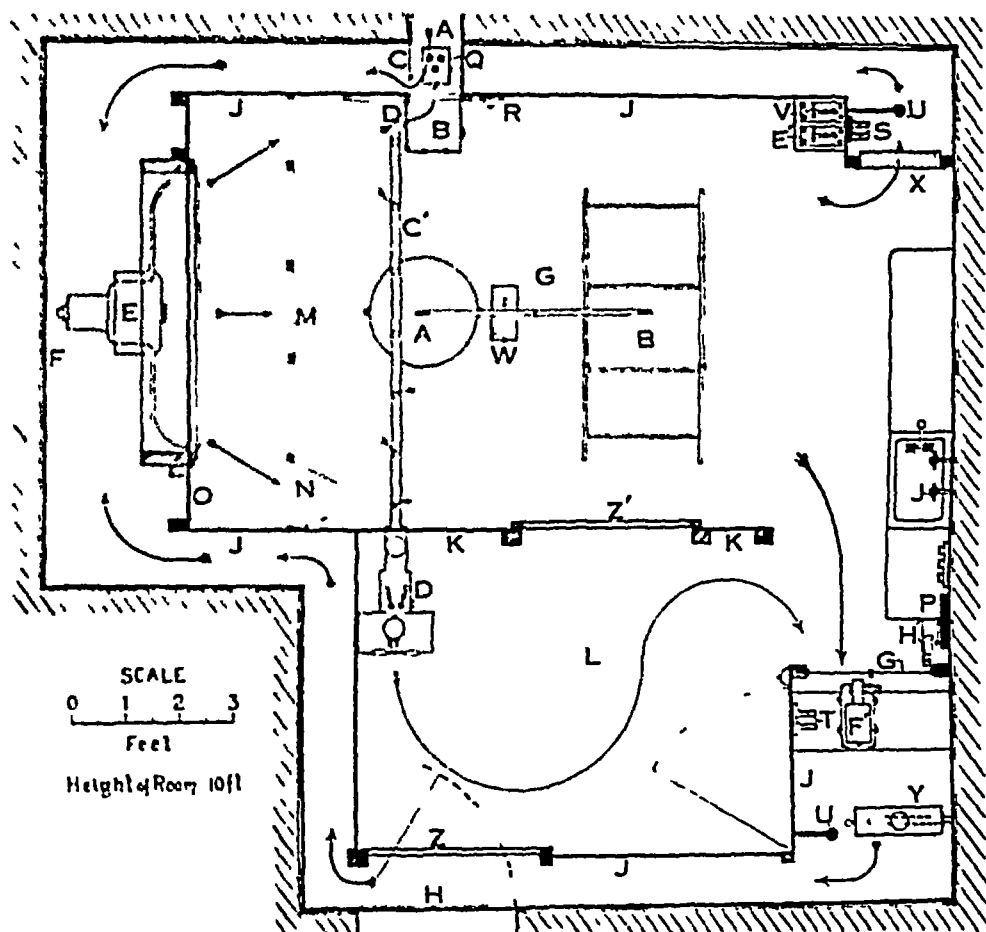


Fig 1 Plan of room 1 or description, see text

(c) *The means adopted for ventilating the room*

The air outside the building communicates with that inside the room through two ducts, A, B, Fig 1, each 30 cm square in section. The lower and inlet-duct, A, opens into the air-jacket, the upper and exhaust duct, B, into the main body of the room. The outer openings of the ducts are guarded by louvres and wire netting, the inner by sliding shutters, C, D. A fan, 54 inch diameter streamline pattern by Messrs Keith and Blackman, Ltd, having a maximum output of 620 cubic metres per min, and driven by an electric motor which takes on full load 1.75 h p, is installed at E, its centre being coaxial with that of the wall F. Its speed is controlled by a variable

resistance, P , so as to give an output of 200 cubic metres per min. This is taken as our standard condition of air movement through the room, and corresponds with a mean air velocity down the experimental chamber G of 45 cm per sec. The sliding shutters, C, D , at the inner openings of the ducts, are so adjusted as to give, at the standard output of the fan, an exchange of 3 cubic metres of air per min, and to maintain the air pressure on the inside of the door H slightly in excess of that on the outside. This last circumstance determines the outward flow of any leakage of air between door and doorcase, and so limits the ingress of air to that passing through the inlet duct from the outside of the building. Air velocities have been measured by means of a small vane anemometer made by Messrs Negretti and Zambra. The efficacy of the above degree of ventilation in preventing cumulation of CO_2 above a level consistent with health and comfort (Pettenkofer (20)) is demonstrated by the figures given in Table I for an experiment in which one man lay at rest on the balance-couch (*see later*), and two men moved slowly about the room and attended to the controls, etc.

TABLE I.

Period between beginning of experiment and taking of gas sample Min	CO_2 in the room air Vols %
95	0.08
158	0.10
248	0.09
310	0.08
367	0.09
504	0.08

The rate of ventilation can of course be readily increased above the standard given above. Such increase, however, will necessitate a correspondingly increased load on the mechanisms by which the entering air is brought into conformity with the standard conditions of temperature and humidity within the room.

(d) *The maintenance and control of the temperature of the air*

With the object of diminishing, so far as seems reasonably practicable, the exchange of heat between the interior and exterior of the room the walls and ceiling are lined with "Celotex"* panels. These are held 1.5 cm

* Celotex is a fibrous material made from sugar-cane and is used commercially for its sound absorbing and heat insulating properties. According to the maker, the Celotex Co. of Great Britain, Ltd. its thermal conductivity is about the same as that of pure cork. It is also highly impermeable to water. The material supplied in panels 7.16 in thick is thus admirably suited to the purposes of the room we are describing.

standard conditions of temperature and humidity within, independent of changing conditions of temperature and humidity without the room. The maintenance of these standard conditions must be automatically controlled through the course of an experiment. Further, the setting of the automatic control must be alterable at will, within wide limits, in order that the effects of a known change in temperature or humidity may be determined.

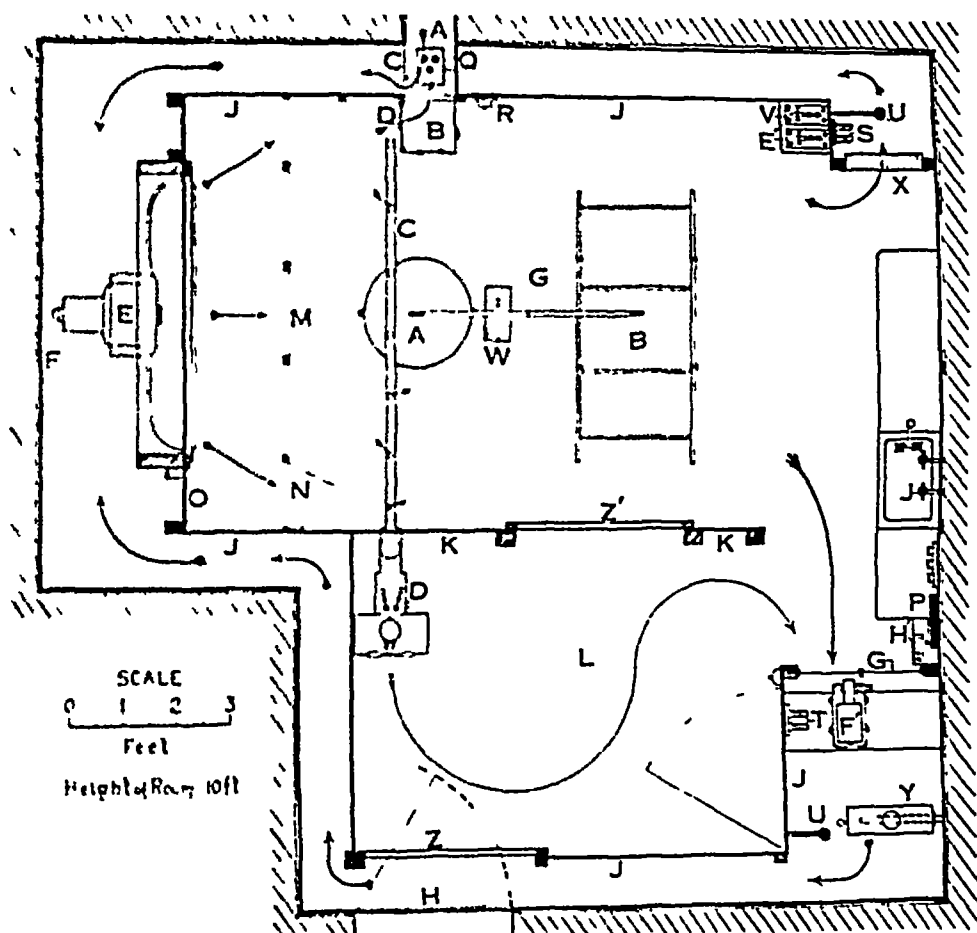


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away from the walls and ceiling by means of battens, the intervening layer of still air forming an additional contribution to effective insulation. All windows in the room have been previously sealed, so that the only remaining channels of communication between the interior and exterior of the room are the two ducts already mentioned, and the doorway H. The concrete floor of the room is covered with cork linoleum 0.5 cm. thick. In order to ensure that the properties of the room-air are held uniform throughout the room, the air, as has already been stated, is maintained in movement by the fan E. The course of this movement is governed by the jackets J, made of Celotex panels vertically disposed between floor and ceiling, and suitably supported by upright strips of wood. The jacket wall is produced, as shown at K, so as partially to divide the room into the experimental chamber G and ante room L. The continuation of the jacket round to the fan-housing ensures that air is drawn by the fan from the air-jackets alone, and maintained in the circulation indicated by the arrows. Currents in the air leaving the fan are largely dispersed by a screen M made of "expanded metal" (0.5 inch mesh) stretching from floor to ceiling and the subject of experiment is shielded from any residual draught by a sheet of calico. Access to the fan and its motor is given by two small doors at N and O.

With the lowest external temperature which is likely to be encountered, say -1° , it will be necessary to raise the temperature of 50 litres of air by 30° every second. This will require 1,890 watts. Three 600 watt heating points are therefore housed in the inlet duct, as shown at Q, and are separately controllable by switches, R. In order to bring the temperature of the room and its contents quickly to 26° , four auxiliary points, each taking 1,000 watts, are used. They are placed as shown, S, T, at the entrances to the air jackets, and so arranged that one, two, three or all four can be brought into action. In the winter months it is found that about an hour is required to bring the temperature of the room up to the standard. This standard having been reached, the temperature is maintained, with or without any of the auxiliary points, by two 600 watt points, U, U, connected in parallel through a 5 amp. mercury-in-hydrogen relay V. In cold weather it is necessary to use one or two of the auxiliary points as a constant source of heat, even when sufficient heat is being supplied at the inlet duct to raise the temperature of the incoming air to 26° . Under such conditions the rate at which heat is lost by conduction is therefore considerably greater than that at which it is simultaneously generated within the room by the human subjects (150 calories per sec. or about 600 watts) and the fan-motor (about 600 watts).

The relay, V, is activated by a toluol-mercury grid placed on a stand, W, in the centre of the experimental chamber. The grid is made from glass tubing, 3 mm. internal diameter, contains 32 c.c. of toluol and causes a movement of the mercury meniscus to the extent of 1.5 mm. for each 0.1° change in temperature. The grid controls the action of the relay by means of a 4 volt cell, and so is the means of switching on or off the heating points

U, U, according to the temperature of the passing air. On an occasion when the external temperature was 11° the relay's action was such that the make and break of the circuit were about equally spaced at intervals of approximately three minutes.

In summer, and especially when a high external temperature is accompanied by a high degree of humidity, it will be necessary, in order to reproduce our standard conditions, to use some means of absorbing heat. The possible degree of this requirement will be apparent from the following rough calculation.

Heat removed in lowering temperature of 50 litres air from 30° to 26° every second	60	cals	per sec
Heat removed in condensing water vapour to convert, per second, 50 litres air saturated at 30° to our standard condition of humidity	500	"	"
Heat production of three men	150	"	"
Heat production of fan-motor	150	"	"
<hr/>			
Total	860	cals	per sec

Under atmospheric conditions, then, as unfavourable as any that are ever likely to be met in London, it will be necessary to have recourse to some means whereby as much heat as 800 cals per sec are absorbed, in order that our standard conditions may be reproduced and maintained. It was decided to attempt this degree of absorption by the passage of water from the cold supply mains, the temperature of which rarely rises above 15° , through a "radiator" across which the air to be cooled is led. From preliminary experiments with a model kindly given us by the Gallay Radiator Co., Willesden, it was calculated that the requisite maximum of heat absorption, viz., 800 cals per sec would be secured by a "radiator" of honeycomb type with a sectional area of 7,500 sq cm and a depth of 10 cm. Such a "radiator" was therefore obtained.

It measures $153 \times 51 \times 10$ cm deep and is fixed in the lower part of the entrance to one of the air jackets as shown at X. Water from the cold supply main is conducted to and from it by means of 2 inch galvanized iron piping and thermometers are placed in the inflowing and outflowing streams. The following observations show that this radiator is capable of absorbing heat almost to the predicted extent under the standard conditions. The room temperature was being maintained constant at 24° when 31 litres of water were passing through the radiator every minute, and heat was being supplied to the extent of 4 000 watts. Stopping the flow of water through the "radiator" and simultaneously switching off 3 000 watts caused a slow rise in the room temperature. The temperatures of the water entering and leaving the radiator 14.4° and 15.8° respectively, showed that 725 cals were being absorbed every second. When the external conditions require it, therefore, and practical experience has confirmed the necessity for its occasional use, the "radiator" is brought into action, the temperature of the room being still controlled by the automatic regulation of the heating points U U.

It has been found that the room temperature, by the means described above, is automatically controllable at $26^{\circ} \pm 0.1$, under such variations in external conditions as have been encountered throughout a year. Moreover, the temperature taken at any one time shows in its distribution through the room no variation greater than 0.1° .

(c) *The maintenance and control of the humidity of the air*

Several means are theoretically available for maintaining in a room adequately ventilated a constant degree of humidity. First, the incoming air may be brought into intimate contact with a saturated aqueous solution of some solute, the selection of the solute being governed by the vapour pressure of its solution, and the solution itself maintained at the temperature of the room by suitable means. Second, the air may be largely depleted of moisture by its passage through brine tanks maintained at a low temperature by the fusion of ice or by other means. The final degree of humidity is then acquired by the controlled addition of water vapour. Third, the requisite amount of water vapour may be added to, or subtracted from, the air by two separate systems. Each of these is brought into or thrown out of action by a mechanism suitably designed to respond to small changes in vapour pressure.

The first method is more suitable for small chambers than for habitable rooms, and does not readily allow variation in the setting of the vapour pressure. The difficulties and cost involved in the application of the principle of the second detract from its practicability. On a hot, humid day, for example, the maintenance of our standard conditions by such means might demand an expenditure of 2,000 cal/s per sec. Attention was therefore given to the third method, its practical development being directed by the following considerations. The demand for added moisture might rise to a theoretical maximum (the outside air being dry) of 0.5 g per sec. The contribution to this demand by the skin and lungs of three men amounts to not more than 0.03 g per sec and can in consequence be disregarded. The raising, every second, of 0.5 g water from say 15° to 100°, and its conversion into vapour requires the supply of 310 cal/s per sec, i.e. 1,300 watts. From the figures given in the British Meteorological and Magnetic Year Book (31), it was deduced that the occasions on which was required an addition of water vapour greater than 70% of the above figure would be rare. A kilowatt heating point was therefore fixed near the bottom of a small galvanized iron cistern (32 × 15 × 30 cm high, Y, Fig. 1), the lid of which was provided with a short chimney through which the generated water-vapour was conducted into the air-jacket of the room. The cistern was enclosed in a wooden box, the walls of which were separated from those of the cistern by a space, 5 cm wide, filled with cotton waste. Through the lid of the box protruded the chimney, and through one side a tube communicating on the one hand with the interior of the cistern, and on the other with a device suitable for maintaining the level of water within the cistern constant. The supply of steam so generated was regulated by the humidity control chamber (1)', Fig. 1) to be described in a moment, working through the intermediation of a mercury-hydrogen relay E'.

The removal of moisture presented greater difficulties than did its addition, those inherent in method being accentuated by the high degree of absorption required under unfavourable external conditions. If the outside

air were saturated with moisture at 30° , the change to our chosen degree of humidity would require, under the standard conditions of ventilation, an absorption of 1 g of water-vapour per second. The magnitude of this requirement will be evident when we reflect that it corresponds with a condensation, in the course of an experiment extending over 8 hours, to more than a cubic foot of water. In order to compass an absorption of this magnitude, consideration was at first given to the controlled passage of air across batteries of glass plates alternately raised from, and lowered into, concentrated sulphuric acid.

The weight, and technical difficulties in the use of an apparatus of such type and of sufficient size* for our purposes, made other methods desirable, and as a result trays of anhydrous CaCl_2 were adopted as our means of controlled absorption of water-vapour. Twelve zinc trays, each $70 \times 79 \times 2.5$ cm deep, with perforations 6 mm in diameter, were placed in a tier occupying the initial part of the air-jacket JY, Fig 1, and guarded by a sliding door G. This could be raised or lowered by a $\frac{1}{2}$ h.p. reversible motor F', the appropriate movement of which was governed by the humidity control chamber D'. A large tinned receptacle collected the water of condensation falling from the zinc trays above. The trays were able to hold in all 46 kg CaCl_2 , the conversion of which to $\text{CaCl}_2 \cdot 4 \text{H}_2\text{O}$ only, would represent an absorption of 30 kg of water-vapour. This amount is sufficient for an experiment of eight hours' duration under such unfavourable external conditions of atmosphere that our room-standards are attained only through an absorption as great as 1 g of water-vapour per second. Measurement showed that under our standard condition of air-movement and with the door G raised, over 42 cubic metres of air passed over the CaCl_2 each minute. An absorption of 15% of the moisture contained in this volume would therefore be adequate for our greatest need. Experience has confirmed our estimate of the efficiency of the above system, in that over a working period of two years no occasion has been encountered on which the means described above were inadequate to reproduce the degree of humidity which had been chosen as our standard.

We pass now to a description of the means whereby the addition or subtraction of moisture by the methods given above is automatically regulated. The regulation is effected by the humidity control chamber D', Fig 1, and of this an illustration is given in isometric projection in Fig 2. Air is drawn by the two-speed electric fan, E, Fig 2, from the experimental chamber G, Fig 1, and conducted by the galvanised iron pipe C', Fig 1, through the partition, K, Fig 1, to the control-box, B, Fig 2. In its passage through this box it passes across two wet- and dry-bulb air thermometers, only one of which, GF, is clearly visible in the figure. The wet bulbs are

* Investigations with a model showed that our requirements would be assured by placing a tank of H_2SO_4 $65 \times 75 \times 85$ cm high in the initial rectangular part of the air jacket JY, Fig 1 and raising and lowering into the acid a battery of 50 glass plates suitably suspended and spaced the cycle of movement occupying 5 minutes.

placed immediately before the opening C, through which the air streams on its way to the fan-box, D, to regain the ante-room, L, Fig 1. The form of, and support for, each wet- and dry-bulb thermometer* are shown in Fig 3. The glass bulbs, CF, BG, are of equal capacity, 65 c c, and connected with each other by the tube FDG. The bulbs are filled with hydrogen under a pressure of 2 atmospheres, the content of the one being separated from that of the other by a mercury seal FDG. This seal is brought into metallic connection with mercury in the tubes H and E by means of platinum wires passing through the points of fusion of the glass tubes. The movement of the mercury seal FDG, itself effected through changes in the difference of

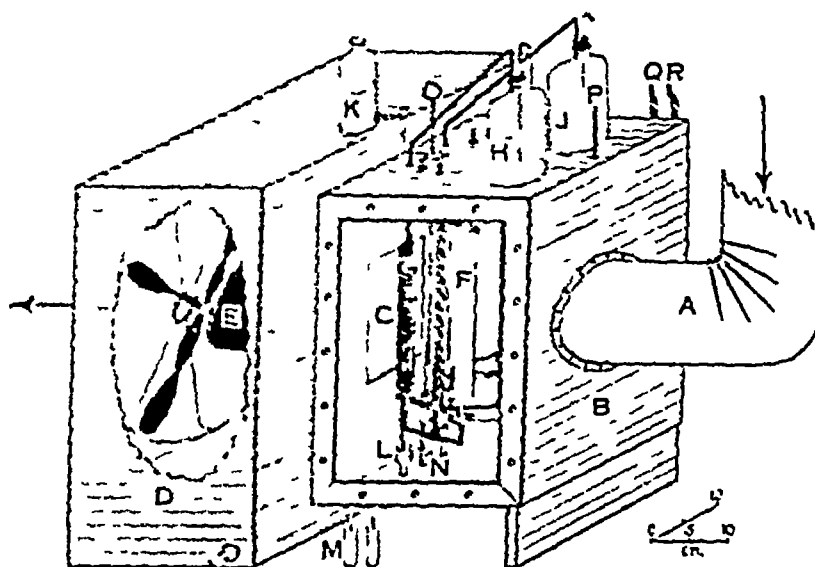


Fig. 2 Humidity control chamber. For description, see text

temperature between B and C, thus becomes the means of making or breaking electrical contact at G. In the case of one pair of bulbs, that in which C is to be the wet bulb and B the dry, the partition of gas between B and C is so arranged that the menisci F and G are on the same level when the temperature of C is maintained about 9° degrees below that of B. In the case of the second pair of bulbs the horizontal disposition of the menisci is realized when B, the wet bulb, is about 9° cooler than C. The cool bulbs, C in the one case, B in the other, are maintained moist by coverings of muslin (G, Fig 2) on to which water is led by drip feeds from the constant pressure reservoirs H and J, Fig 2. Water supplied in excess of that evaporated from the surface of the bulb is conducted by wicks to the small glass funnels L, N, Fig 2, whence it flows into the small receptacles shown at M. Each pair of bulbs is mounted on a steel frame as shown in Fig 3, and suspended by means of the

* These means of controlling the degree of humidity were shown us by Dr R. H. Pickard and his staff at the Shirley Institute, Didsbury. It is a pleasure to acknowledge the great help afforded us through their kindly interest.

rod K from the roof of the control-box. The frame, pivoted at point L, can be tilted to alter its horizontal level by appropriate adjustments of the screw J, against the point of which the plate M is held by the spring N. In this way the level of the meniscus G is alterable at will. The make and break of the platinum-mercury contact on which the activation of the mechanism for the absorption or discharge of water-vapour depends, can be induced, therefore, at varying differences in temperature between B and C, and so at varying degrees of atmospheric humidity. In the case of each pair of bulbs the mercury in E and D is in electrical contact with that in H through the intermediation of an electro-magnet and 4 volt cell, the electro-magnet operating an appropriate relay.

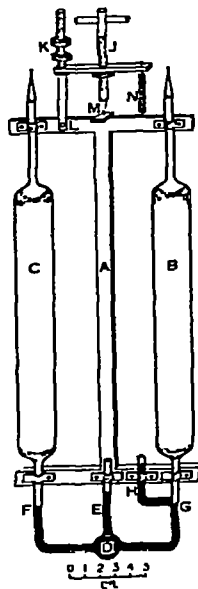


Fig 3 Diagram of wet and dry bulb air thermometer arranged to respond to changes in humidity. For description, see text.

The two pairs of bulbs, then, are suspended as shown in Fig 2. Let us suppose that the inclination of the pair GF is such that at our standard wet- and dry-bulb temperatures (17.7° and 26° respectively) contact at G, Fig 3, is just broken. Any rise in humidity causes contact to be made and so the closure of an electric circuit which itself, through the intermediation of a three-way mercury-in-hydrogen switch, makes contact between R and S, Fig 4. This closure, as we shall see in a moment, sets into operation the electric motor F' (Fig 1) whereby the sliding door G' is raised, and the circulating air allowed to pass across the trays of calcium chloride. The fall in humidity thus effected will, when sufficient in degree, lead to re-breaking of the contact G, Fig 3, and so to the breaking of RS and the making of RQ, Fig 4. This last contact, in its turn, leads to a lowering of the

with the result that the door is lowered until its movement is arrested by the opening of the lower switch L. In this position it remains until a rising humidity brings about the sequence of changes which have already been described as effecting its elevation.

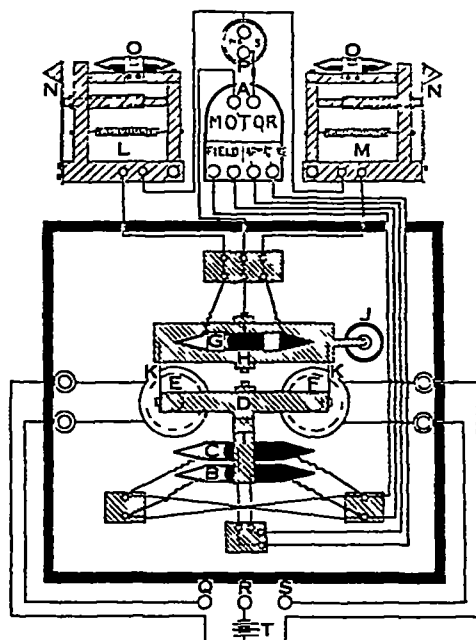


Fig 4 Diagram of relays, reversible motor and switches used for the automatic closing and opening of the calcium chloride compartment For description, see text

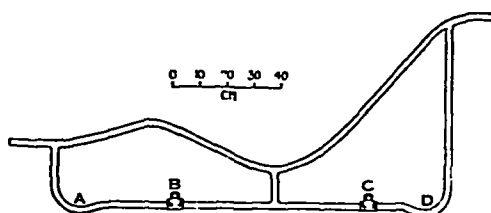


Fig 5 Elevation of tubular frame of couch used in determining the rate of loss of water by man at rest

(f) The measurement of changes in body-weight

We have used for this purpose a suspended beam scale† A' B', Fig 1, carrying on one side a pan A' and on the other heavy chains by which the couch on which the subject lies is supported. The beam is 3 ft 6 in long and is provided at the centre and ends with continuous knife-edges and bearings of hardened steel. The capacity is 100 kg and with this load the sensitivity is such that the scale responds to changes of less than 1 g. The couch consists of a tubular frame 54 cm wide shown in elevation in Fig 5

† This was supplied to us by Messrs De Grave, Short and Co, Ltd London, S E

and on its lower members are clamped the eyes B, C, to which the supporting chains are hooked. Between the upper members are strapped canvas bands 3 to 4 inches wide at such intervals that the comfort of the recumbent subject is assured. The subject lies on the couch in the ante-room L, Fig 1, and is then carried through to the experimental chamber G after the sliding door Z has been drawn back. Between the weighings, the feet (AD, Fig 5) of the couch rest on stools of a convenient height.

The equipment of the room is completed by a standard siphon barometer, a wet and a dry-bulb thermometer near the outside of the inlet duct A, Fig 1, and a chart whereby the readings of these thermometers are converted into terms of aqueous vapour pressure, and so the necessity for abstraction or addition of moisture immediately made known. When desired the respiratory exchanges can readily be determined by either the open (7, 33, 38) or the closed (3) method of measurement.

PART II - "SPONTANEOUS" DIURESIS DURING PROLONGED REST

(a) *Observations and experiments*

The routine adopted in our investigations has been as follows. The subject of experiment arrives in the special room just described about 9.30 a.m. his last meal having been taken at 7.30 the previous evening. The air in the chamber has already been brought to the standard conditions by an assistant. The subject undresses, puts on a pair of thin cotton knickers, and lies on the balance couch, where he remains in a comfortable reclining position for the duration of the experiment. Attached to his garment by a purse string is a wide glass tube tapering at one end, and so leading through a length of rubber tubing to a measuring cylinder below the couch. By this means micturition can occur, and the collection and measurement of the urine can be made with the minimum of disturbance to the subject of experiment. The bladder is emptied at intervals of 15, 20 or 30 minutes, and after a few cubic centimetres from the result of each emptying have been reserved for analysis, the remainder is transferred to a flask suspended from the under carriage of the couch. Series of such flasks and their corresponding analysis bottles are attached to the balance, so that the observed changes in weight during an experiment give directly the course of "insensible loss". A weighing is made every 30 minutes. For this purpose the fan is stopped momentarily, and the weights having been adjusted to the nearest 0.5 g in excess of the equilibrium figure, the time is noted when the swing of the balance needle shows that true equilibrium is attained. The fan is then restarted. At the end of an experiment the tare of the couch and all appurtenances is obtained.

The observations now to be recorded have all been made on the same subject (E B V) although the main phenomenon to which we shall be inviting attention, namely, a delayed diuresis, has been observed in two other normal subjects (P D A II and B S) as well. In Figs 6-10 and in

Table II are shown the changes in urinary secretion observed in a series of five experiments. The first experiment (Fig 6) was begun at 9 45 a m, the subject having had nothing by mouth since dinner the previous evening with the exception of 250 c c of milk at 10 p m. As will be seen from the

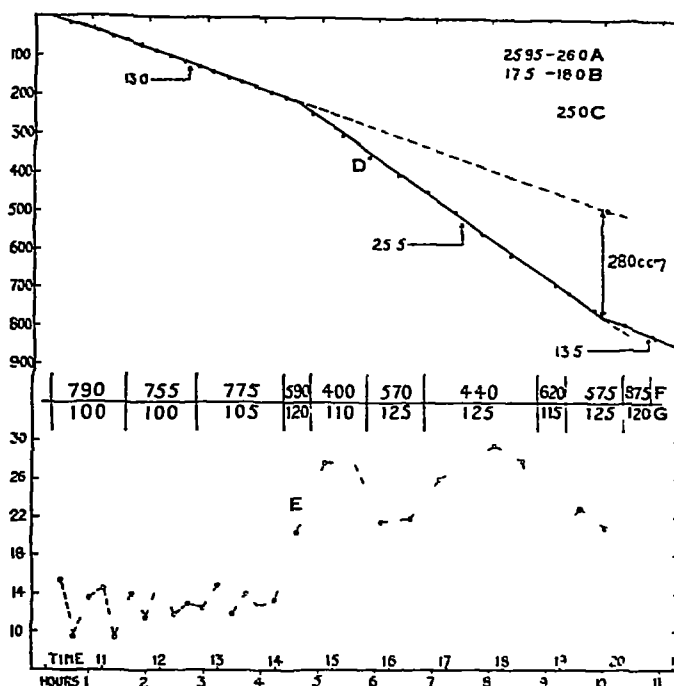


Fig 6 Experiment 1 January the 6th, 1932 A = room temperature, dry bulb and B = room temperature, wet bulb, with their extreme ranges during the experiment C = mean hourly rate of insensible loss of weight in g D = urine loss in c c E = rate of urine flow in c c per 15 min, the time of each plotted point being the midtime of the period during which the sample of urine was collected F = urinary chloride (as NaCl) in mg per 100 c c urine G = urinary chloride (as NaCl) in mg per 15 min Ordinate, above = c c, below = c c per 15 min Abscissa = diurnal time (hours) and period, in hours, from the beginning of the experiment The figures on curve D represent the rates of urine flow in c c per 15 min at the slopes indicated

figure, the rate of urine flow remained fairly steady for so long as 4½ hours, at the end of which time a well-marked diuresis set in, and subsided only between the tenth and eleventh hour of the experiment. The mean rate of urine flow during the diuresis (see Curve D) was nearly double the initial rate of flow. In the next experiment (Fig 7) the rate of urine flow in the early stages of its observation fell, the fall possibly representing the closing ebb of diuresis from 80 c c of milk taken at 8 that morning. However, again in the fifth hour of the experiment a prompt rise in the rate of urine secretion occurred, to be maintained beyond the tenth hour. The onset of diuresis, commonly occurring in the fifth hour (Figs 6, 7 and 9) has been observed both earlier (Fig 10) and later (Fig 8) than thus, though so far as

our observations have shown, always occurring within the period of day to which the experiments are as yet confined, namely, 11 hours

Although, as the figures show, there is considerable variation in the period between the beginnings of the experiments and the onsets of the diureses, in the diurnal times of these onsets, and in the magnitude and courses of the diureses, the various examples of this diuresis exhibit certain features in common. First, the onset is abrupt and, in those experiments in which observation has outlasted diuresis, the close almost equally so

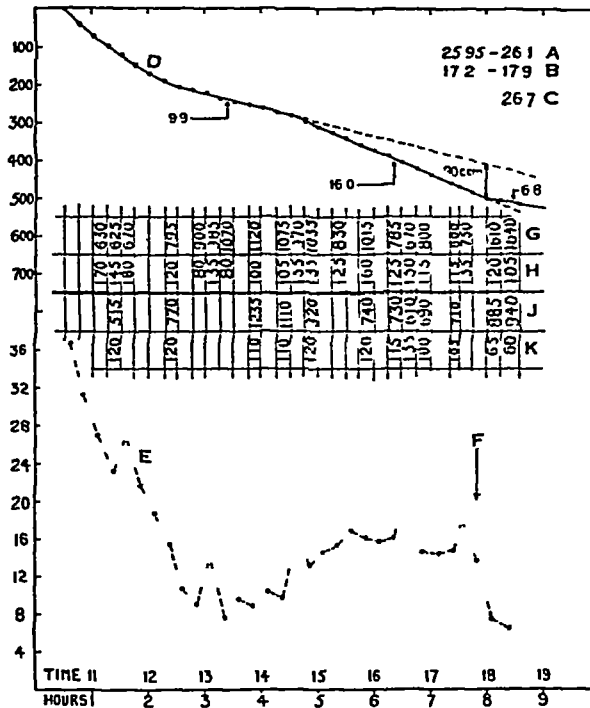


Fig 9 Experiment 4 February the 19th, 1932 A, B C, D, E ordinate, abscissa and the figures on curve D have the same significance as in Fig 6 q v At F 0.1 cc post pituitary extract (Messrs Burroughs and Wellcome 'infundin' containing 10 oxytocic units per cc) was injected subcutaneously G = urinary chloride (as NaCl) in mg per 100 cc H = urinary chloride (as NaCl) in mg per 15 min J = urinary nitrogen in mg per 100 cc K = urinary nitrogen in mg per 15 min

Second, the percentage of chloride and of nitrogen falls, the urine paling during the period of increased rate of flow. Third the diuresis is inhibited by the subcutaneous injection of post-pituitary extract (Figs 9 and 10) the rate of flow falling, with the dosage of extract here used to a value distinctly less than the rate encountered before diuresis set in. Fourth upon the primary wave of increase secondary waves are commonly found imposed, and the reality of their secretory origin is shown by the changes in chemical composition which accompany them (see Figs 6 and 9). Fifth,

the primary and secondary waves appear, so far as experience allows us to judge, independently of any change in sensation or general bodily feeling

There are, moreover, several other points which have emerged from the study of this diuresis, and to the recognition of which the figures in Tables II and III lend aid. Measurement of the rate of insensible loss has shown that this loss reaches a fairly steady state, under the conditions of our experiments, in the fourth hour of rest (Table III). The onset of diuresis, however, though commonly occurring in the hour following this attainment, may, as shown in the Table, find expression some hours before or after. The attainment of steadiness in the rate of insensible loss, a probable index of the rate of heat loss (5), is, therefore, neither the cause nor occasion for the diuresis with which we are dealing. A factor, however, to which the time of onset of diuresis may possibly be related, is the rate of chloride

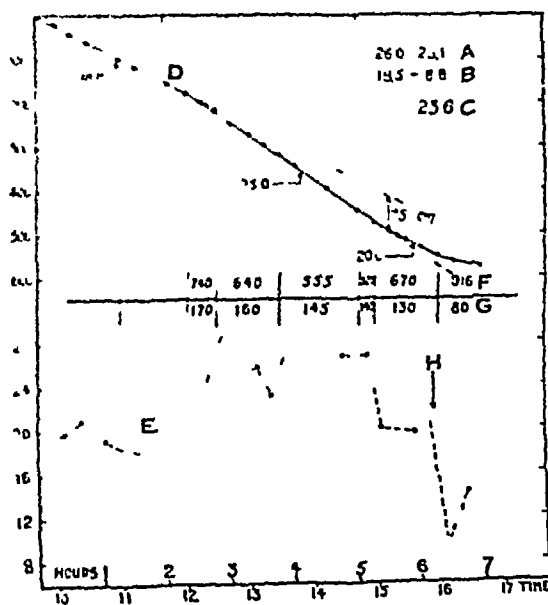


Fig 10 Experiment 5 June the 28th, 1932 A, B, C, D, E, ordinate, abscissa and the figures on curve D have the same significance as in Fig 6 q v F = urinary nitrogen in mg per 100 c c G = urinary nitrogen in mg per 15 min At H 0.1 c c post-pituitary extract (Messrs Burroughs Wellcome and Co "infundin," containing 10 oxytocic units per c c) was injected subcutaneously

excretion during the early part of the experiment, for, as will be seen from Table II and Fig 8, the long delay here encountered was accompanied by a chloride excretion of 180 mg per 15 min, diuresis only occurring when this had fallen to the commonly encountered figure of 120 mg per 15 min, the rate of nitrogen elimination having been steady at 130 mg per 15 min for the preceding three hours. Another point which emerges from the data collected in Table II, is the determination which the pre-diuretic rate of urine flow tends to give the diuretic rate, the ratio between these two values lying between 1.6 and 1.9 in four out of the five experiments.

TABLE II

Date	Time of onset of diuresis hours from beginning of experiment	Duration of diuresis min	Extra water administered c c	Extra water administered c c per 15 min	Ratio of water excretion c c per 15 min			Ratio B/A	Ratio of chloride excretion (as NaCl) mg per 15 min		Ratio of nitrogen excretion mg per 15 min	
					Before diuresis A	During diuresis B	After diuresis C		Before diuresis	During diuresis	Before diuresis	During diuresis
01.32	1.5	325	280	13.0	13.0	25.5	13.5	1.0	100	120	—	—
22.1.32	1.5	> 330	165	7.5	10.5	17.5	—	1.6	80	110	145	145
5.2.32	0.5	40	40	15.0	18.7	33.0	18.0	1.7	180	110	130	130
10.2.32	1.5	> 210	00	0.5	0.0	16.0	0.8*	1.0	100	135	110	120
28.6.32	2.5	180	75	0.2	18.8	25.0	20.0	1.3	—	—	170	145

*This is the ratio following a subcutaneous injection of 0.1 c c post pituitary extract (Messrs Burroughs, Wellcome "infundin," 10 oxytocic units per c c)

TABLE III

Date	Time (hours) from the beginning of the experiment											
	1	1	2	2	3	3	4	4	5	5	6	6
6.1.32	38.0	31.0	27.0	27.0	25.0	21.0	21.0	23.0	23.0	21.0	23.0	25.0
22.1.32	31.0	27.5	26.5	26.5	21.0	26.0	26.0	21.0	21.0	23.5	23.0	22.5
5.2.32	37.0	33.5	28.0	28.0	27.0	23.0	23.0	20.0	20.0	20.0	—	—
10.2.32	34.0	30.0	27.0	27.0	21.5	20.5	20.5	27.5	27.5	27.0	—	—
24.0.32	33.5	26.5	23.5	23.5	21.0	22.0	22.0	21.0	21.0	—	—	—
Mean	35.5	30.0	26.5	26.5	21.5	21.0	21.5	21.5	25.0	25.0	—	—

To show the mean hourly rate of measurable loss of body weight in grams. The means of the figures in the five experiments are given in the last row. D signifies the hour period when "spontaneous" diuresis commenced.

In these two points only have we been able to detect amongst the data so far obtained, evidence suggesting a positive association between the diuresis itself and its contiguous phenomena. Indeed the variation encountered in the degree of diuresis demonstrates a failure in adequate control of conditions before or during the period of observation, and the elucidation of the cause of the diuresis rests, therefore, on one's ability to secure, first, its recurrence in constant proportions, and second, its variation by the imposition of known changes in environment. To this end, and with the suggestion which the long delay in the onset of diuresis gives, namely, that parenteral rather than enteral factors are responsible for the diuresis, it becomes desirable to see, first, whether the delayed diuresis occurs at the usual diurnal time when the period of observation begins in the evening instead of the morning, second, whether the diuresis occurs during the waking state when this becomes nocturnal and the sleeping state diurnal, third whether in observations prolonged over 36 hours, the diuresis recurs during the second day, and fourth, whether the time and course of the output of water during the second day can be influenced by the time and course of a water diuresis evoked during the first. Observations bearing only on the first of these four questions are described in the present paper.

The observations were made on the same subject as had been the earlier ones, and were undertaken with the object of seeing whether the diuresis occurred at the usual diurnal time when the period of experiment included the preceding night. Two experiments have been made*. In the first the subject took a light supper at 19.30 hours and reached the room at 22.30 hours, the temperature and humidity of the room air having been stabilized already at the usual values. Having changed into pyjamas, he lay on blankets on a camp bed adjacent to the balance couch, and slept restfully till 8.15 the following morning. Slips were then substituted for the pyjamas, the balance couch was slowly mounted, and observations on urine flow and insensible loss were begun. The mean rate of urine flow from 9.10 to 13.10 was 10.6 c.c. per 15 min., the concentration of chloride (as NaCl) being greater than 1,000 mgm. per 100 c.c. urine. Diuresis then set in to reach, during the succeeding 90 minutes, a mean rate of 19.2 c.c. per 15 min., the chloride concentration meanwhile falling to 700 mg. per 100 c.c. During the next 90 minutes the diuresis subsided to a rate of 13.6 c.c. per 15 min. and this change was accompanied by a rise in the urinary chloride to over 1,000 mg. per 100 c.c. In this experiment, then, a diuresis with the usual characters occurred at the usual diurnal time. The experiment, however, was not entirely trustworthy as the basis of argument against the diuresis being conditioned by a differing environment before diurnal observations were begun, since, first, a small amount of active movement was necessary in mounting the balance couch, and second, the light clothing worn during the night was removed before the observations of the daytime were

* For help in both experiments we have been indebted to Professor Otto Kraye, without whose happy co-operation these prolonged observations would not have been made.

made. Indeed the insensible loss during the first hour of its measurement, from 9 30 to 10 30, was 32 g, after which it fell to a mean value of 22.2 g per hour over the succeeding six hours. A second experiment was, therefore, undertaken with the object of excluding any contribution which the factors of skin covering and active movement might have made towards the late diuresis. The results are shown graphically in Fig 11. The subject of

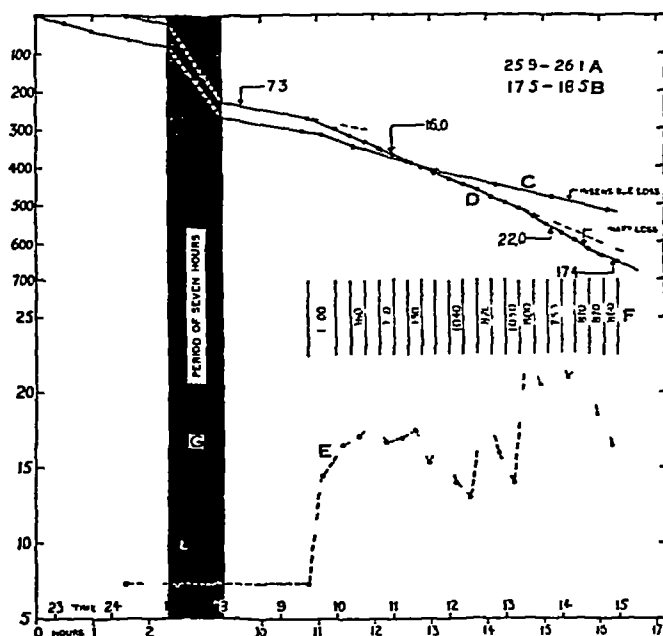


Fig 11 Experiment 6 July the 10th 11th, 1934. A, B, D, E, F, abscissa and the figures on curve D have the same significance as in Fig 6 q v. C = insensible loss in g. G = period of seven hours. Ordinate, above = g (insensible loss) and c.c. (urine) below = c.c. per 15 min. Throughout this experiment the subject was wearing a light pyjama suit.

experiment took a light supper at 19 30 hours on July the 10th, 1934, and arrived in the chamber at 22 hours. He undressed, put on a light pyjama suit, lay on a blanket supported by the balance couch and later enjoyed a light refreshing sleep. From 22 40 to 00 22 weighings were made at intervals of approximately 30 minutes. At 22 55, 175 c.c. warm tap water were drunk. At 00 17 the bladder was emptied, and the subject then settled to sleep. He awoke about 9 25. After the bladder had been emptied weighings were started again and the urine was collected at the end of each 15 minute period. Observations were continued till 15 00 hours on July the 11th the subject then having lain on the balance couch under constant environmental conditions, and in a state of undisturbed repose, for a period of 17 hours.

If we follow the course of urine secretion given in the figure we see that a matutinal tide of water excretion flows from the mean nocturnal value, 7.3 c.c. per 15 min., to reach a level of 16.0 c.c. per 15 min. which is maintained

till 13 15. The diuresis with which we are familiar now sets in, the rate of urine excretion reaching a mean value of 22.0 c.c. per 15 min. over the next five quarter-hourly periods. The rate then falls towards its earlier level.

Another fact of interest emerges from the data collected in the figure. The rate of insensible loss from 0 20 to 9 20, approximately the period of sleep, was 26.1 g. per hour. The simple transition to the waking state was followed over the next two hours by a mean hourly loss of 43 g., a large increase over the nocturnal rate. This high rate of insensible loss was not maintained, however, the hourly rate from 11 50 to 14 50 being steady at 35 g. A fall in the rate of insensible perspiration during nocturnal sleep has been described by Benedict and Wardlaw (6), but the observations given above to the effect that the change to the waking state is followed by a temporary rise in the rate of insensible loss to a value in excess of the succeeding diurnal rate is, so far as we are aware, new.

This experiment demonstrates, then, that the diuresis which our earlier experiments disclosed occurs independently of such changes in external environment and variations in voluntary muscular activity as had immediately preceded the morning period of observation.

(b) Discussion of the previous observations, and experiments, thereby suggested, upon the influence of the pituitary gland on diuresis.

Various changes of recognised association with increased urine flow occur to one as the possible cause or occasion for the phenomenon under discussion. The change from the sleeping to the waking state (15, 21, 22, 30) as also that from the standing to the lying posture (15, 22, 34), leads to a rise in the rate of urine flow. Since, however, such rise occurs during the first hour following the change in conditions, the phenomenon we are here presenting cannot be due directly to these changes. Moreover, as the experiment given in Fig. 11 demonstrates, the diuresis occurs when there has been no change in posture for so long a period as 14 hours before its onset. Neither can it find its cause in a falling loss of water through vapourization such as would be produced by a fall in skin temperature (17, 18) attributable to the naked state. The tenability of such an explanation is excluded by the degree and course of vapourization-loss already given. Moreover, no feeling of cold has been experienced in the chamber by the subject of experiment—indeed on one occasion the room temperature was maintained at 28°C. and the late diuresis still occurred. Explanation, therefore, in terms of a rise in metabolism following a fall in body temperature becomes equally improbable.

The possibility, however, must be considered of the diuresis being due to a diurnal and qualitative change in metabolism. Now the resting oxygen consumption of E. B. V. is about 230 c.c. per min. The rate of excretion of nitrogen by the kidney is about 10 mg. per min. At constant "non-protein oxygen consumption" of 176 c.c. per min. and on the basis of assumption that during the combustion of 1 g. of fat, of carbohydrate and of protein,

11.36 and 34 g respectively of water are freed (39) a complete change of non-protein metabolism from fat to carbohydrate would be associated with an increase of 11.3 c.c. per 15 min in the amount of water freed. At constant "non-protein calorie output" a complete change of this character would be associated with an increase of 9.6 c.c. per 15 min. It is inconceivable, therefore, even in the absence of respiratory quotient measurements, that the increased output of water can be accounted for solely by qualitative changes in metabolism. Moreover, if we assume a fasting R/Q of 0.82, and the tenability of the figures given above for the amounts of water freed during the combustion of fat, protein and carbohydrate, we can calculate that 8.6 g of water are freed for elimination every 15 min. This rate is below the minimum rate of urine flow in any of the experiments here recorded, so that, leaving out of account even the pulmonary water loss, amounting in E.B.V. to between 5 and 6 g per 15 min, the subject is running into "water debt". This being so, there seems no clear reason why an increased elimination should occur.

We have been unable to find, therefore, on the basis of any associated manifestation, a rational interpretation of the diuresis. When, however, we consider the features which its various examples exhibit in common and to which we have already referred, an interpretation, in so far as concerns the proximate cause, is readily found through the hypothesis which assigns to the pituitary gland an essential participation in the chain of processes through which the output of water by the kidney is physiologically determined. This function of the kidney is brought by the hypothesis to direct dependence on the concentration, in the blood, of the substance to which the anti-diuretic activity of post-pituitary extract is due. The hypothesis has lately received extension (14) in order to cover recently acquired facts with respect to water diuresis, and to embrace phenomena of possible relation thereto.

With this hypothesis in mind it became of interest to form an estimate of the amount by which the concentration of post-pituitary anti-diuretic substance in the blood must be lowered in order to produce an increase in water secretion of the order of that encountered in our experiments. For this purpose varying amounts of post-pituitary extract* were injected intravenously into the subject on whom the observations already recorded had been made. The extract used ("infundin") was obtained from Messrs. Burroughs, Wellcome and Co., samples from one batch only being employed and between the experiments the extract was preserved at 0°. Its content in total solids, as determined by drying the extract at 110° was found to be 400 mg per 100 g water, and it had been standardised by the makers to contain 10 oxytocic units per c.c. When injections were to be given the original extract was diluted with sterile Ringer's fluid immediately.

* For simplicity of presentation we have given the dose in terms of volume of our fluid extract. We were interested to know the largest possible fall in the plasma in the concentration of post-pituitary anti-diuretic substance to which the observed diuresis could be attributed. Figures in excess of this value are assumed in our calculations by expressing the concentration in terms of the total solids in our extract.

beforehand, the dilution being of such degree that the selected dose was contained in a volume of 0.5 c.c. In two earlier experiments in which the requisite dilutions were made and autoclaved beforehand, the results were invalid because of the readiness with which the anti-diuretic fraction becomes inactivated by such treatment, a fact which was pointed out to us by Dr G. W. Theobald. The dose of extract was injected into an ante-cubital vein, and on each occasion the period of injection was 70 seconds. The preparation of the fluid to be injected was invariably carried out in the antechamber I, Fig. 1, so that the subject of the experiment was unaware whether he was receiving a control injection of Ringer's fluid or an injection of pituitary extract.*

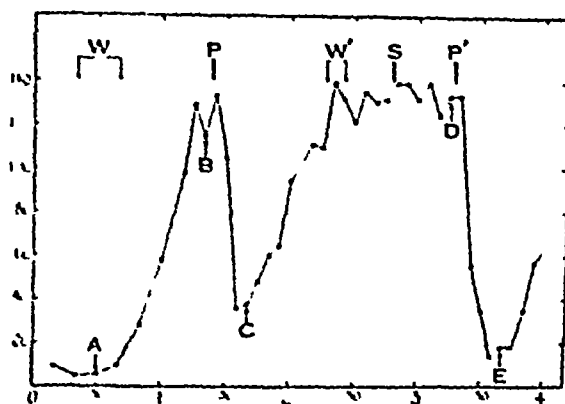


Fig. 12 Experiment 7. Water diuresis and its inhibition by post pituitary extract. At W 1,000 c.c. tap water were drunk. At P and again at P' 0.0002 c.c. "infundin" (Burroughs, Wellcome and Co.) was injected intravenously. At W' 450 c.c. water were drunk. At S 0.5 c.c. Ringer's fluid was injected intravenously. Each point on the curve represents the rate, in c.c. per 15 min., of secretion of the volume of urine collected in the interval between this time and that of the preceding point on the curve. Ordinate = c.c. per 15 min. Abscissa = time in hours and minutes. The amounts of chloride (as NaCl) in the urine at A, B, C, D, and E were 1,250, 115, 155, 110 and 980 mg. respectively per 100 c.c. urine.

The experiments were undertaken under environmental conditions similar to those of the earlier ones, that is to say the subject arrived in the chamber about 9.30 a.m., undressed, and lay on the balance couch during the whole period of observation. The dry-bulb temperature in each experiment was maintained at 26°, and the wet-bulb at 19.5° in the former of two experiments to be recorded, and at 18.5° in the latter. But whereas in the earlier experiments no water was taken, in these diuresis was produced by 1,000 c.c. of tap water drunk at a temperature of 37°. The bladder was emptied voluntarily at the end of each five or ten minute period.

The results of two experiments performed under the conditions just described are recorded in Figs. 12 and 13. If we restrict our attention for the time to the first response to pituitary extract in each experiment, we see

* The preparations of the fluid and the intravenous injections were all made by Professor Otto Krayer. It is a pleasure to record our deep sense of gratitude for the help which he so willingly gave.

that 0.0002 c.c. (Fig. 12) caused, over a period of 55 min., a temporary retention of 172 c.c. of water, this figure representing the difference between the volume of water actually excreted in the period, and that which would have been excreted in the same period had diuresis persisted at the plateau level. It corresponds of course with the area of the anti-diuretic response on the curve of urine-flow, and will be referred to as the anti-diuretic volume. Similarly in the experiment recorded in Fig. 13 the injection of 0.0001 c.c.,* under conditions closely akin to those pertaining to the previous experiment, produced an anti-diuretic volume of 44 c.c. spread over a period of 30 min. The mean fall in rate over the 55 minute period of the first experiment when 0.0002 c.c. was injected was therefore 3.1 c.c. per min., that over the 30 minute period of the second experiment when 0.0001 c.c. was injected, 1.5 c.c. per min. The close proportionality of these figures suggests, at high rates of water excretion, and at high water loads, the assumption which

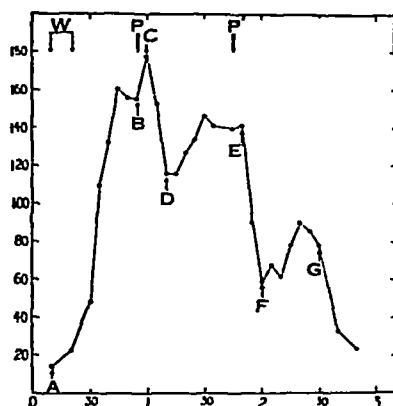


Fig. 13 Experiment 8. Water diuresis and its inhibition by post-pituitary extract. At W 1,000 c.c. tap water were drunk. At P and again at P' 0.0001 c.c. 'infundin' (Burroughs Wellcome and Co.) was injected intravenously. Each point on the curve, and the ordinate and abscissa have the same significance as in Fig. 12 q.v. The amounts of chloride (as NaCl) in the urine at A, B, C, D, E, F and G were 78.5, 90, 85, 125, 75, 205 and 190 mg. respectively per 100 c.c. urine.

we shall now make—that, the greatest changes in rate of urine flow being sub-maximal, there is a direct proportionality between a single increment of post-pituitary anti-diuretic substance in the plasma and the mean fall in rate over the period of anti-diuresis on the one hand, and between a single decrement of the same substance and the mean rise in rate over the period of diuresis, on the other. For simplification of argument we shall also assume that at maximum rates of water secretion the concentration in the plasma of post-pituitary anti-diuretic substance is zero. If we now turn to the data comprised in Figs. 6 to 11, we can deduce from the values and periods of excess secretion of water, that the mean rate at which the excess water is

* That water diuresis in man is inhibited to a demonstrable degree by pituitary extract given intravenously in doses of this order has already been shown by Theobald (32).

eliminated is 0.6 c.c. per minute. Now the fall in rate given above, viz., 1.5 c.c. per min., is produced by the presence in the plasma of the anti-diuretic substance associated in the original extract with 4×10^{-7} g. of solute. On the basis of the assumptions already made, therefore, the mean diuretic rate encountered in our experiments, viz., 0.6 c.c. per min. is caused by the disappearance from the plasma of the anti-diuretic substance associated in the original extract with 1.6×10^{-7} g. of solute. The weight of the subject of experiment is 58 kg. If we assume his plasma volume to be 2,500 c.c. this disappearance of anti-diuretic activity corresponds in terms of the total solids in the extract with a fall in their concentration of one part in 1.5×10^{10} parts of plasma. But that this calculation over-estimates, and probably grossly so, the decrement in anti-diuretic substance to which the diuresis may be attributed, is made likely by two considerations. First, the anti-diuretic factor in the solute can be considered as forming a small fraction only of the total weight of substance. Second, we have evidence (see Table IV) that the initial diminution in the rate of water secretion produced by post-pituitary extract is greater at low water loads than at high.* The relevant data, collected in Table IV, are taken from experiments 7 and 8 (Figs. 12 and 13).

TABLE IV

Time from beginning of last water drinking to beginning of intravenous injection Min	Amount of post-pituitary extract injected c.c.	Approximate excess water load at time of injection c.c.	Maximum depression in rate of urine flow c.c. per 15 min
62.5	0.0002	737	97
60	0.0002	353	120
46	0.0001	643	45
95	0.0001	188	82

In these experiments the last inhibitions of urine flow were not followed by, nor traced to recovery to the plateau level of diuresis, so that we could not derive a mean fall in rate as the basis of comparison of the final with the initial response in each experiment. The figures for the maximum depression in rate of urine flow during the initial inhibitory responses in the two experiments suggest, however, that at the same load of excess water, this depression, when sub-maximal, is proportional to the dose of extract injected. We may interpret these results as expressive of a greater sensitivity, to post-pituitary anti-diuretic substance, of the processes within the kidney which are involved in water secretion, when the water load is small than when it is large. We should expect, therefore, that an increased

* In a private communication Dr. G. W. Theobald tells us that he has obtained in dogs evidence which leads to the same conclusion.

elimination of water such as we have observed under the conditions of our experiments (*see* Table II), would be produced by a smaller fall in concentration of anti-diuretic substance in the plasma than that derived from the results of experiments on the inhibition of water diuresis at high water loads, and which corresponds with a fall of one part of the total solids of the extract in 15 milliard parts of plasma

During the course of experiments on the inhibition of water diuresis by pituitary extract given intravenously, we have encountered a fact which

TABLE V

Time interval Min	Urine secreted during interval c c	Time of beginning and of end of injection Min sec	Interval between end of injection period and beginning of period first showing inhibition of urine flow Min sec	Amount of extract injected c c
0 5 5 10 10 15 15 20 20 25	43 0 38 5 45 0 35 0 12-0	12 30 13 40	1 20	0 0002
0 5 5 10 10 15 15 20 20 25	40 5 41 5 44 5 44 5 18 5	16 40 17 50	2 10	0-0002
0 5 5 - 10 10 15 15 20 20 25	47 0 42 0 45 0 44 0 27 5	15 10 16 20	3 40	0-0001
0 5 5 10 10 15 15 20 20 - 25 25 30	53 5 52-0 54 0 50 5 51 0 38 5	15 5 16 15	~ 3 45	0-0001
0 - 5 5 10 10 15 15 20 20 - 25	47 0 39 0 46 5 47 5 30-0	15 10 16 15	3 45	0-0001

we think of sufficient importance to record now, though we have not sufficient data to make profitable a discussion of its significance. On mentioning the fact to Dr Theobald we found that he had already met the same phenomenon in experiments on both man and the dog, namely a period of the order of 3 minutes between the time at which post-pituitary extract is injected into the blood stream and the time at which the response of the kidney begins. Thus latent period has been evident on every occasion on which we have injected the extract, and when careful records of urine flow have been made

The data are given in Table V. If we assume that an interval of 30 seconds, probably a generous estimate, elapses between the end of the injection period and the time at which the drug reaches the kidney, we see that when 0.0002 c.c. was injected the minimum latent period was 50 sec. in one case and 1 min. 40 sec. in the other. When 0.0001 c.c. was injected the minimum latent periods were 3 min. 10 sec., 3 min. 15 sec., and 3 min. 15 sec. in the three observations which have been made. In the fourth observation recorded in the table, little inhibition could have occurred till about the 7th or 8th minute from the end of the injection period. Whether the latent period is due wholly or in part to slow diffusion of the active principle from plasma to renal cells, to cumulation of the principle to an active concentration at these cells, or is, rather, a normal occurrence in that sequence of events within the cell which are involved in the inhibition of water secretion, we have no evidence on which a judgment can be based.

The interpretation of the facts reported in this paper in terms of the pituitary hypothesis still leaves ungiven the reason for the occurrence of a fall in the secretory activity of the pituitary gland in the day some hours after a posture of rest has been assumed, and for its variation to the degree which the observations on the urine flow suggest. Further experiment is necessary on the lines already indicated in order that facts relevant to this problem may be acquired, and especially to establish whether the diuresis which we have described is to be regarded rather as the expression of a diurnal variation in the processes involved in water secretion, than as a phenomenon specifically conditioned, in time of onset and degree of response, by previous administration of water.

SUMMARY

1. A room is described in which the ventilation and the temperature and humidity of the air are under independent control, and in which the weight of the human subject can be followed with accuracy.
2. At the standard conditions of ventilation, air temperature and humidity chosen for our experiments, the dry- and wet-bulb temperatures are automatically controlled within 0.2° and 0.5° respectively. With the balance employed the weight of the human subject is determined with an error of less than 1 g.
3. When, under our standard conditions, the fasting human subject assumes the recumbent posture at about 10.00 hours, a "spontaneous" diuresis is found to begin some three to six hours later.
4. The duration of the diuresis has varied from 40 minutes to more than 3½ hours. The onset is abrupt, and in those experiments in which observation has outlasted diuresis the close is almost equally abrupt.
5. The diuresis is accompanied by a fall in the concentration of chloride and of nitrogen in the urine. It is inhibited by post-pituitary extract.

6 The diuresis occurs independently of such changes in external environment and variations in voluntary muscular activity as commonly precede the morning period of observation

7 The onset of diuresis is not related to the attainment of steadiness in the rate of "insensible loss" of body weight

8 Transition from the sleeping to the waking state in the morning is followed by a temporary rise in the rate of "insensible loss" to a value in excess of the succeeding diurnal rate

9 In the course of the ordinary diuresis following water ingestion, marked inhibitory responses were given in man by the intravenous injection of 0.0001 c c of a post-pituitary extract containing 10 oxytocic units per c c and 400 mg solid matter per 100 g water. The concentration, in the plasma, of post-pituitary anti-diuretic substance which causes partial inhibition of maximal diuresis in man is, therefore, much less than 1 part in 6 milliard, seeing that a fraction only of the solute in the extract can constitute the anti-diuretic factor (Confirming Theobald, 1934)

10 When such doses of post-pituitary extract as cause partial inhibition of a maximal diuresis are injected intravenously, there is a delay of some 1 to 4 minutes before the diminution in rate of urine flow begins

11 Facts are presented which suggest that the kidney is less sensitive to post-pituitary anti-diuretic substance at high water loads than at low

12 On the hypothesis that the output of water by the kidney is physiologically determined through variations in the activity of the pituitary gland, the "spontaneous" diuresis encountered in our experiments is ascribed to a fall in the concentration of post-pituitary anti-diuretic substance in the plasma of less than 1 part of substance in 1.5×10^{10} parts of plasma

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THE CEREBROSPINAL FLUID PRESSURE IN ARTERIAL HYPERTENSION *

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MANY observers since Quincke (23) have described a raised cerebrospinal fluid pressure in hypertension, but until recently there has been no systematic study of the subject, and it has been impossible adequately to interpret the scattered results. The work here reported was undertaken to determine the cerebrospinal fluid pressure in a representative series of patients with high blood pressure, and to find out the significance and cause of the differences observed. Meanwhile Shelburne, Blain and O'Hare have published a similar study (24), and their conclusions are amplified and largely confirmed here. These authors found that papilloedema, headache, and renal impairment occurred more commonly in patients having cerebrospinal fluid pressures above 200 mm H₂O, than in those with lower pressures. The systemic venous pressure was not raised in their cases, and they were unable to account for the raised cerebrospinal fluid pressure, though they noted that it was frequently associated with a diastolic blood pressure of over 130 mm Hg.

Cases and methods

The cases investigated were of persistent high blood pressure without oedema †. The cerebrospinal fluid pressure was measured in a vertical manometer tube of 1 mm bore, and corrected for capillarity, precautions were taken to have the patient horizontal, to avoid loss of fluid, to avoid postural compression of the neck veins, and to allow the cerebrospinal fluid pressure to settle to a steady level. In all cases except Case 12 (where impaction of the hind-brain in the foramen magnum was found after death), respiratory and pulse oscillations were present, and the pressure readings given in this paper are the means of these limits of oscillation. The arterial blood pressure was recorded by the auscultatory method during lumbar puncture. Before or after lumbar puncture, the systemic venous pressure was measured by noting in the supine patient the level at which the jugular

* Work undertaken on behalf of the Medical Research Council

† A number of cases were referred to me because of retinal lesions and for these I wish to thank Mr Neame, Sir John Parsons, Mr Foster Moore and Mrs Martin.

veins collapsed. Occasionally the venous pressure was measured in the median basilic vein by the method of Moritz and Tabora, giving results similar to those obtained by inspection of the neck veins. All venous pressures are expressed in cm. water above the angle of Louis.

The colloid osmotic pressure difference between blood and cerebrospinal fluid was estimated by a slight modification of Verney's method (25), using plasma inside the capsule and cerebrospinal fluid as the dialysate. The plasma was obtained immediately after lumbar puncture by withdrawing, without congestion, 10 c.c. of venous blood into 0.1 c.c. of saturated potassium oxalate solution. The apparatus was set up in duplicate or triplicate and readings usually agreed to 5%. Since comparative rather than absolute values of the osmotic pressure were required, no account was taken of the plasma dilution observed by Cope (5) and attributed by him to stretching of the cellophane membrane.

Variations of cerebrospinal fluid pressure in the individual

In six patients (Cases 4, 19, 25, 27, 31, and 35, Table I) the lumbar pressure varied by 30 mm. water or less, when measured on two or more occasions. In five others (Cases 2, 3, 14, 15, and 16) the variations were greater. In Case 15 aphasia developed suddenly on 30.6.34, and lasted 8 days; on 1.7.34 the lumbar pressure was 334 mm. water, five days later it had fallen to 270 mm., and 29 days later to 227 mm. The fall of pressure in this case may be correlated with the gradual regression of the disturbance produced by an acute cerebral vascular lesion. In Case 14 the spinal pressure fell from 270 mm. on 17.5.33 to 150 mm. on 19.6.33, and the blood pressure dropped from 216/155 to 178/115 during the same period. In the other cases no explanation could be offered for the variations in lumbar pressure.

The relationship of the cerebrospinal fluid pressure to clinical features of the disease

In the 37 patients with high blood pressure who were examined, the cerebrospinal fluid pressure ranged from 80 to 400 mm. water. When the cases are arranged in order of cerebrospinal fluid pressure, as in Table I which summarises their chief features, it is found that they fall naturally into two groups presenting a number of striking differences. Group 1 consists of patients with spinal pressures above 250 mm., and Group 2 of those with lower pressures. In addition, 3 patients (Cases 14, 15 and 16) had on different occasions pressures both above and below 250 mm.; they have been placed in Group 1a, and presenting as they do features to some extent intermediate between the two groups, will be omitted from the following discussion.

Age. The patients of Group 1 range in age from 15 to 49 years, the average age for the group is 35 years. In Group 2 the age varies from 44 to 71 and the average age is 56 years.

Duration of life The 13 patients of Group 1 all died at a period varying from 1 day to 19 months after lumbar puncture. Of these cases 10 died in uræmic coma, 3 died suddenly in convulsions, probably or certainly to be attributed to cerebral hæmorrhage. The average duration of life for the patients comprising the group was 4 months.

Of the 21 patients of Group 2, 5 have died, 14 are known to be alive at the time of writing and 2 are untraced, but no death certificates have been issued. Of the 5 cases that have died, one died of carcinoma of the breast, and one of aneurysm of the abdominal aorta of syphilitic origin. In 3 of the cases death was due to the hypertensive disease itself, uræmia being the cause in one, a cerebral vascular lesion in two cases. The average duration of life for the 19 patients traced was greater than 20 months.

Impairment of renal function Renal function was assessed by the urea concentration test and by estimating the blood urea. The cases may be divided into—those in which renal function was normal, as shown by a maximum urea concentration in the urine of 2.0% or more; those in which renal function was slightly impaired, as shown by a maximum urine urea concentration of less than 2.0% with a normal blood urea; and those with renal failure and nitrogen retention, as shown by a raised blood urea. Of the 13 cases in Group 1, 2 had normal renal function, 4 had impaired renal function and 7 had gross renal failure with nitrogen retention at the time of lumbar puncture. One (Case 9) of the two cases with normal function, and two of those with impaired renal function (Cases 3 and 11) died later in uræmia. In Group 2 on the other hand renal function was normal in 14 cases, slightly impaired in 4 cases, and renal failure with nitrogen retention occurred in 2 cases. Uræmia has not subsequently occurred in any of the patients of Group 2 who had normal or slightly impaired renal function at the time of lumbar puncture.

There is thus a pronounced tendency to a severe and fatal involvement of the kidneys in those hypertensive patients who have a greatly raised cerebrospinal fluid pressure. On the other hand those hypertensive patients who have a normal or only slightly raised spinal pressure do not usually develop renal failure.

The fundus oculi The retinal lesions in high blood pressure are usually divided by British ophthalmologists into the forms albuminuric and arteriosclerotic retinitis (21),* although it is recognised that cases occur that are intermediate in type. Arteriosclerotic retinitis was first differentiated from the albuminuric form by Foster Moore in 1917 (20) who found it to have a better prognosis and was regarded as having the following characteristics:

* A similar division is usually made in America though often under a different terminology. Thus of the 3 different ophthalmoscopic pictures recognised in hypertension by Fisher and Oppenheimer (8) arteriosclerotic retinopathy corresponds to arteriosclerotic retinitis and malignant hypertensive retinitis and choked disc can be considered a form of albuminuric retinitis. The German *leichte atypische Retinitis* (17) seems to correspond to arteriosclerotic retinitis.

TABL

Case and diagnosis	Age and sex	Date	Pressure			H ^o	
			C S F mm H ₂ O	Arterial mm Hg	Venous cm H ₂ O		
Group 1 1 Chronic nephritis	19 I	24 5 32	400	svst 240 diast 160	- 5	5	
2 Chronic nephritis	31 F	8 5 31 21 5 31 25 5 31 10 7 31	290 340 350 295	190 180 206	+ 1 - 1 + 1		
3 Chronic nephritis	15 I	28 1 31 27 2 31 28 2 31 5 3 31 19 3 31	275 260 300 260 300	246 215 215 214 214	160 0	6	
4 Malignant hypertension	41 M	6 5 31 7 5 31	305 290	230 250	150 160	0	8
5 Malignant hypertension	38 M	21 6 32	300	198	130	- 1	4
6 Chronic nephritis	36 I	2 12 32	300	234	150	- 1	6
7 Malignant hypertension	49 M	21 7 31	275	220	140	- 1	10
8 Chronic nephritis	37 I	19 1 32 18 5 32	270	220	130	- 1	5
9 Malignant hypertension	47 F	7 6 32 11 2 33	270	266	140	- 1	9
10 Chronic nephritis	37 I	11 4 31	265	236	145	0	8
11 Chronic nephritis	42 F	7 9 31 3 11 31	252	270 265	180 160	0	8
12 Periarthritis nodosa	22 M	3 10 32	250	194	120		7
13 Chronic nephritis	47 M	8 8 31	250	220	150	+ 2	8

I

Blood urea mg %	Urea conc test	Fundus oculi					Macular star		After history
		Arterio sclerosis	Papilloedema		Exudates				
			L	R		L	R		
377		+	++	++	Numerous large woolly, R and L	+	+		Died uremia 25 5 32
32	1 75	0	++ 2D	++ 3D	Numerous large woolly, R and L do	+	0		Retinitis resolved 26 5 32 Died convul sions 21 12 32
		0	do	do		—	+		
56	0 7	+	++ 3D	++ 3D	Numerous large woolly, R and L	+	0		Died uremia 9 7 31
45	2 0	++	+	+	Several ill-defined, R and L	0	0		Died convulsions 16 8 31
370	1 3	+	+	+	Numerous large woolly, R and L	+	+		Died uræmia 22 6 32
200		++	2D	2D	0	0	0		Died uremia Feb, 1933
54	1 6	++	'	'	Large ill defined small well-defined, R and L	0	+		Died cerebral hæmorrhage Nov, 1933
95	1 6	+	?	'	Large woolly, R and L	0	0		Died uremia 24 6 32
		+	4D	3D	Increased	+	+		
54	2 1	++	?	'	Large well-defined, R and L	0	—		Died uremia 11 4 33
100	0 95	++	++	++	Numerous large woolly	—	—		
280	1 2	+	+	+	Large woolly, R and L	—	—		Died uræmia 19 4 34
47	1 9	+	0	0	Several ill-defined R and L	0	0		Died uremia 14 11 31
100		+	—	+	Increased	0	0		
172		0	+	+	Several large woolly R and L	0	0		Died uræmia 9 10 32
112	0 6	—	1 5D	1D	Numerous large woolly R and L	—	—		Died uræmia 25 11 33

TABLE

Case and diagnosis	Age and sex	Date	Pressure				Hb %
			CSF mm H ₂ O	Arterial mm Hg		Venous cm H ₂ O	
Group 1a 14 Malignant hypertension	41 M	17 5 33	270	syst 216	diast 155	— 1	
		7 6 33	170	184	140	0	
		19 6 33	150	178	115	0	
15 Hypertension ? malignant	65 F	1 7 31	334	216			
		6 7 31	270	230			
		30 7 31	227	220			
16 Essential hypertension	60 F	8 11 32	200	196	140	0	88
		9 2 34	220	260	140	+ 3	
Group 2 17 Essential hypertension	53 F	21 6 32	240	276	140	+ 1	102
18 Essential hypertension	46 F	17 6 32	210	194		0	86
19 Essential hypertension	56 F	7 10 31	207	230	170	2	
		23 11 31	210	224			
20 Essential hypertension	47 F	21 6 33	200	276	160	0	102
21 Chronic nephritis	49 F	22 3 32	190	184	100	1 5	
22 Essential hypertension Diabetes	65 F	26 7 33	190	184	98	0	90
23 Essential hypertension	68 F	2 12 33	185	244	125	+ 1	
24 Essential hypertension Carcinoma of breast	69 F	17 9 31	180	234		+ 2	
25 Essential hypertension	58 M	27 5 31	175	174		0	
		20 5 31	170	180		0	
26 Essential hypertension	59 F	9 5 31	170	200	110	+ 1	82
27 Essential hypertension	58 F	6 11 31	165	240	120	0	75
		30 5 34	135	250	120	— 1	90

I—continued

Blood urea mg %	Urea conc test	Fundus oculi					After history
		Arterio sclerosis	Papilloedema		Exudates	Macular star	
36	35	++	L 2D	R 3D	Small well-defined, R and L	L 0 R +	Died cerebral hemorrhage 21 1 34
		++	2D	3D	do	0 +	
		++	2D	3D	do	0 +	
42	29	++	?	?	Few moderate size, R and L	0 0	Died cerebral hemorrhage 16 10 32
45	26	++	0	0	Few punctate, R and L	0 0	No papilloedema June, 1934 Unchanged Nov, 1934
		++	0	½D	Several large hard exudates, L	0 +	
		++	0	0	Several punctate, L	0 +	Unchanged 12 9 33 Alive 24 5 34
50	23	0	0	0	0	0 0	Unchanged 15 9 34
54	19	+	0	0	0	0 0	Untraced No death certificate issued before 30 9 33
36	21	++	0	0	Several punctate, L	0 0	Unchanged 12 7 34
99	13	0	0	0	0	0 0	Untraced No death certificate issued before 30 9 33
46	22	+	0	0	3 punctate L	0 0	Exudate R and L 27 9 34
51	24	++	0	0	Numerous punctate, L	0 0	Unchanged 23 5 34
	18	0	0	0	0	0 0	Died carcinoma October, 1931
	25	0	0	0	0	0 0	Unchanged 19 7 34
36	21	+	0	0	0	0 0	Unchanged 24 5 34
40	18	++	0	0	Several punctate R and L	— 0	Unchanged 1 10 34
45	16	++	0	0	A few punctate R	0 0	

TABLE

Case and diagnosis	Age and sex	Date	Pressure				Hb %
			C S F mm H ₂ O	Arterial mm Hg		Venous cm H ₂ O	
Group 2 28 Essential hypertension	74 M	21 7 33	165	svst 200	diast 105	0	98
29 Essential hypertension	68 F	30 8 33	165	160	90	0	
30 Essential hypertension Aneurysm abdominal aorta	52 M	11 11 31	165	226	130		
31 Essential hypertension	44 F	24 1 31 8 9 31 9 9 31	155 143 160	208 216 194	130	+ 1 + 1 + 1	66
32 Essential hypertension	48 F	15 9 31	150	174	110	+ 1	
33 Chronic nephritis	51 F	8 10 32	145	230	140	+ 5	
34 Essential hypertension	52 F	11 7 31	135	294	140	0	
35 Essential hypertension	63 F	6 4 32 7 10 33	135 130	166 174	96 98	— 1 0	
36 Essential hypertension	53 M	17 5 33	125	155	100	— 2	64
37 Essential hypertension	54 M	13 4 32	80	194	112	0	

The retinal lesion consists of small sharply defined white spots, usually unilateral, always associated with retinal arteriosclerosis, but never with retinal oedema and rarely with swelling of the disc, a macular star figure is uncommon and is composed rather of discrete dots than of radiating lines

In albuminuric retinitis a raised cerebrospinal fluid pressure has been observed by Cushing and Bordley (3, 6), Larsson (16), and McAlpine (18), Fishberg and Oppenheimer (8) on the other hand state that this is not invariable. Shelburne, Blum and O'Hare (24) found that papilloedema was present in 19 out of 20 cases of hypertension with a lumbar pressure greater than 200 mm water, but in only 2 out of 30 cases with a lower lumbar pressure, they made, however, no other distinctions between the retinal changes found in their two groups

I—continued

Blood urea mg %	Urea conc test	Fundus oculi						After history
		Arterio sclerosis	Papillœdema		Exudates	Macular star		
45	2 6	+	L 0	R 0	Several punctate, R and L	L 0	R 0	Alive 19 7 34
54	2 1	+	0	½D	Several punctate, L	0	0	Optic atrophy L eye 1 11 34
90	2 0	0	0	0	0	0	0	Died 1 1 32
45	2 4	0 0	0 0	0 0	0 0	0 0	0 0	Unchanged 1 11 34
45	2 0	0	0	0	0	0	0	Unchanged 1 7 34
180		+	+	++	Large ill-defined, R and L	+	0	Died uræmia 23 10 31
39	2 0	+	0	0	One, R	0	0	Died cerebral hæmorrhage 22 5 33
	1 9	0 0	0 0	0 0	0 0	0 0	0 0	Unchanged 24 5 34
27	2 2	+	0	0	0	0	0	Alive 1 7 34
	2 0	0	0	0	0	0	0	Died Dec 1932 cerebral thrombosis

In the series of cases here investigated a close association has been found between the type of retinal lesion and the height of the cerebrospinal fluid pressure. These retinal changes are summarised in Table I*.

In Group 1 all the patients presented, at the time of lumbar puncture or subsequently, the changes characterising albuminuric retinitis, namely bilateral swelling of the nerve head, large ill-defined exudates in both retinæ, and a macular star figure. The complete picture was not always present, particularly at the first examination, but the subsequent course of the lesions resolved all doubt as to the type of retinitis to which they conformed. Two illustrative cases in which the nature of the retinal lesion was originally in doubt may be cited.

* My examinations of the fundus oculi were checked by Mr. Neame, ophthalmic surgeon to University College Hospital, to whom I wish to express my gratitude.

In Case 8 the cerebrospinal fluid pressure was 270 mm water on 19 4 32, both discs were hazy, and there was a number of large ill-defined exudates in both eyes but no star figure. On 18 5 32, the optic discs were swollen by 3 and 4 diopters, both retinæ were cedematous and showed numerous large ill-defined exudates, and a partial star figure was present at each macula. She died in uræmic coma on 24 6 32.

In Case 9, Sir John Parsons found retinal arteriosclerosis and a number of small sharply defined white spots in both eyes and a macular star in the right eye in August, 1931, a diagnosis of arteriosclerotic retinitis was made, renal function was then normal. In June, 1932, the cerebrospinal fluid pressure was 270 mm, the discs were hazy but not definitely swollen, the white spots were of larger size but still well defined, and the star figure persisted in the right eye, renal function was normal. In February, 1933, there was gross swelling of both discs, and of the surrounding retinæ, there were numerous large coalescent greyish yellow exudates, and both macular regions were covered with white masses forming irregular sheets, renal failure was then advanced and the patient died in uræmic coma in April, 1933.

In Group 2 on the other hand, 12 patients had no lesion of the retina apart from arteriosclerosis, and 8 had arteriosclerotic retinitis, one patient (Case 33) was exceptional in having albuminuric retinitis, but in her the low lumbar pressure may have been due to dehydration from uræmic vomiting. Of the 8 cases of arteriosclerotic retinitis, only one presented cedema of the nerve head, and this was unilateral and transient. The "exudates" were unilateral in 6 cases, bilateral in 2, and were smaller and more sharply defined than in Group 1. Cedema of the retina was never observed. The only two cases in which there was any doubt as to the type of retinitis are briefly as follows.

Case 27 was referred from Moorfield's Eye Hospital in November, 1931, with the diagnosis of albuminuric retinitis in the right eye, the left being atypical, the cerebrospinal fluid pressure was 165 mm. At that time she presented in the right eye a few small shining spots to the temporal side of the disc and a macular star figure composed of radiating lines and irregular sheets, in the left eye there were only a few shining spots near the disc, arteriosclerosis was pronounced in both eyes but there was no cedema of either nerve head or retina. In August, 1933, the spots had disappeared from the left eye, but the macular star remained unchanged in the right. In June, 1934, a few small discrete dots round the right macula were the sole remnants of the original retinitis. The urine remained free from red cells and casts throughout, and renal function was essentially the same in 1934 as in 1931.

Case 29 was sent by Mr. Neame in July, 1933, as a case of arteriosclerotic retinitis with 1 diopter swelling of the left disc. In August, 1933, the cerebrospinal fluid pressure was 165 mm H_2O , the left disc was swollen $\frac{1}{2}$ diopter, and was surrounded by radiating hæmorrhages, there were numerous small, sharply defined, punctate or oblong yellowish-white areas

in the left retina. In the right eye there were no lesions apart from arteriosclerosis, which was present in both eyes. The swelling of the left disc disappeared by September, 1933, being replaced by consecutive optic atrophy. In July, 1934, the conditions of the fundi and of the patient generally, were unchanged.

In 1908 Cushing and Bordley (6) suggested that albuminuric retinitis is due to raised intracranial pressure. Their chief evidence was the improvement in the retinal condition witnessed after repeated lumbar puncture, (3) (6), and the complete regression of the retinitis after cerebral decompression in one case of their own (6) and one of Bramwell's (4). But in one of the cases improving after lumbar puncture, and one of the two that were decompressed, the retinitis followed pregnancy, under which circumstances the lesions are frequently transient (21)*. While a number of recent authors (16, 18) concede that papilloedema is due to raised intracranial pressure, Cushing and Bordley's hypothesis has not been accepted in its original form because it fails to account for the presence of "exudates" in albuminuric retinitis and their usual absence in tumour of the brain. The precise nature and cause of these exudates remains obscure, but it is probable that they are essentially similar in both forms of the retinitis of hypertension. Thus Foster Moore (20) was unable to distinguish any fundamental histological differences between them, and cases are occasionally met in which the lesions, initially of the arteriosclerotic type, finally present the typical picture of albuminuric retinitis (*e.g.* Case 9). The distinguishing feature seems to be the presence in the albuminuric form and the absence in the arteriosclerotic form of more or less widespread neuro-retinal oedema, and the observations here described suggest that this in turn is a simple consequence of the level of intracranial pressure. Thus in the albuminuric form the intracranial pressure is at or above the level at which in other disorders fluid accumulates in the nerve head and retina (1), whereas in the arteriosclerotic form the pressure is less raised or is normal.

Types of hypertension. From what has already been said it is evident that the two groups of cases present numerous differences in their main clinical features, and it is perhaps to be anticipated that they will conform to two essentially different types of hypertension, the one grave, the other relatively benign. Until the etiology and mechanism of hypertension are known, no classification can be satisfactory, but the cases of Group 1 all correspond to the pale hypertension, and those of Group 2 (except Cases 21 and 33) to the red hypertension of Volhard (26). On the basis of the classification originally proposed by Volhard and Fahr (27) and now generally

* In two cases of the present series this was so. Thus in Case 2, the retinitis began 2 weeks and had resolved 1 year, after parturition. In Case 6 albuminuric retinitis developed 1 month before term in May, 1925. In August, 1926, the retinitis had disappeared leaving only pigmented spots in the retina. The discs were again swollen but there were no retinal exudates in December, 1932, during terminal renal failure. It may be noted that cerebral decompression has not always proved successful in relieving albuminuric retinitis. Thus Grant (11) has recently described 2 cases in which decompression failed to improve the retinitis, but in both the intracranial pressure also remained raised.

accepted, there were, in Group 1, 8 cases of chronic nephritis 4 of malignant hypertension, and 1 of periarteritis nodosa. In Group 2 there were 19 cases of essential hypertension and 2 of chronic nephritis. The occurrence of undoubted cases of chronic nephritis in both groups shows that the types of hypertension cannot be sharply differentiated by the cerebrospinal fluid pressure. It seems that a cerebrospinal fluid pressure above 250 mm. water is an expression of some advanced stage of disease, which is reached eventually in chronic nephritis and malignant hypertension, but rarely, if ever, in essential hypertension.

Relation to convulsions, coma and headache. A disturbance in the functions of the brain commonly occurs in patients with high blood pressure as a result of rupture or thrombosis of a cerebral vessel, such disturbances are usually fatal or more or less permanent. Occasionally however, the disturbances though profound, are transient. For example, there may be one or more convulsions, followed by coma which disappears in a few hours and leaves no abnormal signs in the central nervous system. These attacks are termed pseudo-mæmia (26) or hypertensive encephalopathy (22) and are in the absence of a known chemical cause, commonly attributed to œdema of the brain (Volhard (26)). Since the patients rarely die during these attacks the evidence for this view of their origin is chiefly circumstantial. A common argument is the presence of a raised cerebrospinal fluid pressure in such cases (19, 26), but this does not bear examination for two reasons. In the first place, although the only 3 patients of this series experiencing these attacks had cerebrospinal fluid pressures of 250 to 350 mm. water yet the other 10 patients with equally raised pressures had no attacks. In the second place, in two of these (Cases 2 and 3) the cerebrospinal fluid pressure was found to be essentially the same in and out of the attacks. It is evident therefore that the disturbance producing the attacks commonly fails to influence the cerebrospinal fluid pressure. Nevertheless in the third case (Case 12) evidence of cerebral œdema was found during life and confirmed after death, the brain being impacted in the foramen magnum. Gorke and Toppich (10) and Blackfan and Hamilton (2) have each described a case in which a similar lesion was found at autopsy, though in neither case were the cerebral disturbances so profound as in that described here. The three cases are briefly as follows —

Case 2. A woman of 34 years, lost the sight of her right eye and her ability to speak and became drowsy 3 hours before the onset of her third labour on 30.3.31. Labour was otherwise uneventful and lasted 6 hours. Her systolic blood pressure was 190 mm. Hg, she had slight œdema of the legs and arms, and her urine contained much albumen, the blood urea was 43 mg. %. She remained drowsy until 3.1.31 when she recovered, by this time the œdema had disappeared but the hypertension persisted, the fundi were normal. On 7.4.31 the optic discs were hazy and there was one large exudate in the left eye. On 2.5.31 she had two hemiplegic attacks associated with drowsiness and aphasia and each lasting several minutes, the first affected the left, the second the right side of the body. After the attacks there were no abnormal nervous signs. On 7.5.31 albuminuria retinitis was fully developed in both eyes. About 4 p.m. on 25.5.31 she became drowsy and confused and there was conjugate deviation of the eyes to the right. Lumbar puncture at 7 p.m. was followed by two generalised convulsions and coma which lasted about 12 hours. Two similar attacks occurred on 30.5.31 and 30.6.31. Albuminuria retinitis was disappearing on 10.10.31, and had resolved by 20.5.32 leaving consecutive optic atrophy.

and pigmented spots in the retina Hypertension and the presence of albumen and casts in the urine persisted throughout, but there was never any rise in the blood urea She died suddenly in convulsions on 2 12 32 The following lumbar pressures were recorded

Date	Cerebrospinal fluid pressure in mm water	Symptoms
8 5 31	290	Headache
21 5 31	340	No symptoms
25 5 31	350	Coma A convulsion followed immediately on lumbar puncture
10 7 31	295	No symptoms

Case 3 A girl of 15 years became drowsy with the onset of her menstrual period in October, 1930, and later became comatose and had 3 epileptiform convulsions Coma lasted 56 hours in all and recovery from it was complete The systolic blood pressure was 190 mm Hg the blood urea 90 mg %, and the urine contained red blood corpuscles, granular casts and much albumen There was no oedema Albuminuric retinitis was present in both eyes The blood urea fell to 50 mg % at the end of October but the blood pressure remained raised During her menstrual period of November she experienced severe headache, but neither coma nor convulsions With the onset of menstruation on December, 22nd, 1930 she became irritable and complained of headache On the 23rd she became comatose and had thirteen generalised convulsions each lasting about 2 minutes, Babinski's sign was positive on both sides Recovery from this state was complete on December the 25th, 1930 On January the 28th, 1931, during the next menstrual period she again became comatose and had convulsions, recovery was complete, apart from severe headache, by January the 30th In the menstrual period of February, 1931, she became drowsy for 2 days and complained much of headache but had no fits During the disturbances of December, January, and February, the blood urea was normal, and the blood diazo reaction was negative From this time there were no further convulsions, nor did she again become comatose until an acute exacerbation of the nephritis led to death in uremia on July the 9th, 1931 The following lumbar pressures were recorded

Date	Blood pressure in mm Hg	Cerebrospinal fluid pressure in mm water	Symptoms
28 1 31	246	275	Coma Convulsions preceded and followed lumbar puncture Menstruating
27 2 31	215	260	Drowsy Headache Menstruating
28 2 31	215	300	Drowsy Headache Menstruating
5 3 31	214	260	No symptoms Menstruating
19 3 31	214	300	No symptoms Not menstruating

Case 12 A seaman aged 22 became delirious and had a fit followed by coma on 1 10 32 When admitted to hospital on 2 10 32 he was very drowsy and suffering repeated convulsions but presented no other abnormal signs in the central nervous system He had a systolic blood pressure of 190 mm Hg and a blood urea of 110 mg % the urine contained albumen granular casts and blood There was no retinitis At 1 a.m. on 3 10 32 20 c.c. of cerebrospinal fluid were removed by lumbar puncture the pressure was not measured but was thought to be increased Five epileptiform fits followed in quick succession and by 2 a.m. the temperature had risen to 105°F At 11 30 a.m. the temperature had fallen to 102°F he was a little less drowsy and lumbar puncture was repeated The fluid rose to a height of 250 mm in the

manometer tube, and showed small pulse but no respiratory oscillations. After removal of 1 c.c. of fluid the pressure fell to 160 mm, jugular compression raised the pressure slowly to 180 mm at which it remained when the compression was released. Impaction of the brain in the foramen magnum was diagnosed and no further fluid removed. He was treated by intravenous injections of 25% glucose, and had no more fits, though remaining more or less drowsy. The blood urea rose to 250 mg % on 6.10.32, and on 7.10.32 both discs were swollen, and large exudates were present in both retinæ. He died on 8.10.32. Autopsy showed periarteritis nodosa affecting the heart and pancreas slightly and the kidneys extensively. The brain was tense and its convolutions flattened, a "pressure cone" was present, the medulla and cerebellum being pressed backwards and moulded to fit the foramen magnum. The cerebral arteries and brain substance showed no macroscopic abnormalities.

In two of the patients just described (Cases 2 and 3) the cerebrospinal fluid pressure was essentially unaltered during the presence of headache. A similar observation was made on Case 4, a man aged 41 suffering from malignant hypertension. On 6.5.31 this patient complained of severe headache and the spinal pressure was found to be 305 mm, on the following day he had no headache and the spinal pressure was 290 mm. While there

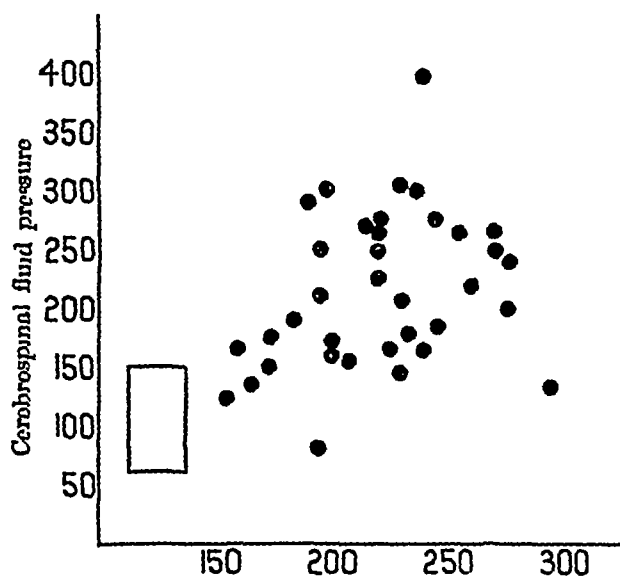


Fig 1 Systolic arterial pressure

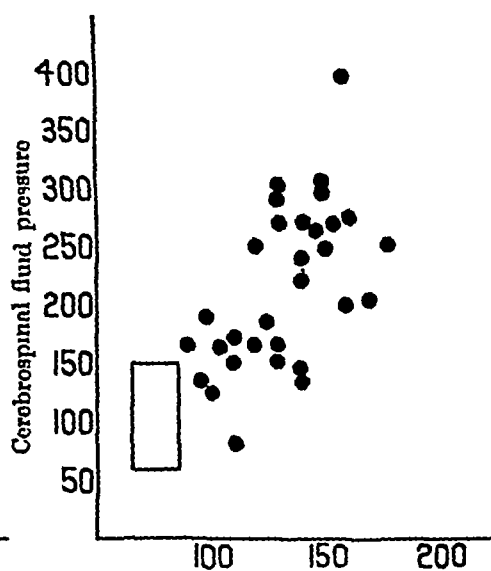


Fig 2 Diastolic arterial pressure

Figs 1 and 2 The cerebrospinal fluid pressure (in mm CSF) is plotted against the systolic arterial pressure (in mm Hg) (Fig 1) and the diastolic arterial pressure (Fig 2). In each figure the rectangle represents the range of variation of these pressures in normal subjects.

is no evidence that headache in these cases was due to raised intracranial pressure, yet it is probable that the pain was due to some form of mechanical change in the cranial cavity, for in all three patients the pain was immediately increased by withdrawal of cerebrospinal fluid.

The cause of raised cerebrospinal fluid pressure in hypertension

In attempting to find the cause of the raised spinal pressure, the following factors have been investigated.

Venous pressure In most cases the venous pressure was normal. From Table I it is evident that cerebrospinal fluid and systemic venous pressure are unrelated.

Arterial pressure In Figs 1 and 2 the values for the cerebrospinal fluid pressure have been plotted against the values for systolic and diastolic arterial pressures. The cerebrospinal fluid pressure is unrelated to the systolic pressure, but appears to be related to the diastolic pressure, though not exactly.

Anæmia That anæmia may be a factor in determining the cerebrospinal fluid pressure is suggested by the case of a male aged 33 and suffering from bleeding piles, who had a cerebrospinal fluid pressure of 210 mm water and an arterial pressure of 105/65 mm Hg on 14.11.31 when the hæmoglobin content of his blood was 30%. On 18.12.31 when his hæmoglobin was 80% the cerebrospinal fluid pressure was 150 mm water and the arterial pressure 108/75 mm Hg. In the present series anæmia was commoner in Group 1 than in Group 2, and may in some cases have contributed to the raised spinal pressure, but there was no close relationship.

Vascular permeability In 6 cases of Group 1 the protein content of the cerebrospinal fluid varied from 0.04% to 0.14% and averaged 0.07%, in 10 cases of Group 2 the protein content varied from 0.02% to 0.08% and

TABLE II

Case	C S F pressure mm water	Colloid osmotic pressure difference Blood/C S F cm water
J C (7)	275	30.0
M L (9)	270	20.5
J L (14)	270	20.5
A C (17)	240	33.4
M W (18)	210	32.6
A W (20)	200	34.8
E C (27)	165	28.0
H P (28)	165	28.8

averaged 0.035%. The cell counts of the fluid were normal in all cases. This suggests that the cerebral capillaries were slightly more permeable to protein in the patients of Group 1 than in those of Group 2.

Colloidal osmotic pressure differences between blood and cerebrospinal fluid The colloid osmotic pressure difference between blood and cerebrospinal fluid has been determined in 8 cases and the results are shown in Table II. It will be seen that there is no constant relationship between this value, and the cerebrospinal fluid pressure.

Retention of chemical substances by the kidneys In 2 patients of Group 1 (Cases 4 and 9) the urea concentration test gave normal values, and in 4 patients (Cases 2, 3, 7, 11) there was no nitrogen retention. Without further evidence, the retention of chemical substances by the kidneys cannot be considered as responsible for the raised spinal pressure.

Comment Although other factors must be concerned, the diastolic arterial pressure is the only one actually found to show a close relationship to the cerebrospinal fluid pressure, and this relationship might result in one of two ways. In the first place a raised cerebrospinal fluid pressure might produce a raised blood pressure. Dixon and Heller (7) have shown in the dog that when the absorption of cerebrospinal fluid is hindered by intracisternal injection of kaolin the resultant raised intracranial pressure is accompanied by a rise of blood pressure. Heller (12) has supposed that the mechanism in certain cases of human hypertension may be similar, and in support of his view he has used a statement of Kahlers (15) that in some cases of hypertension, removal of cerebrospinal fluid produces a fall of blood pressure. In the cases here investigated, removal of cerebrospinal fluid has produced no fall of blood pressure either as an immediate or as a remote effect, Hulse (14), Shelburne, Blain and O'Hare (24), and McAlpine (18) have described similar results. The evidence is, therefore, against this view. A second possibility is that the cerebrospinal fluid pressure is determined by the diastolic arterial pressure, or more probably by the mean arterial pressure to which the diastolic pressure approximates more closely than does the systolic value*. Such a relationship could be explained as follows. The available evidence suggests that high blood pressure is due to an increased peripheral resistance resulting from arteriolar constriction. It is, however, unlikely that this constriction affects the cerebral vessels to any extent, since, in animals at least, they react very weakly to such agents as sympathetic stimulation and adrenalin (9) and do not participate in the generalised vasoconstrictor response to the carotid sinus and depressor reflexes (13). The cerebral capillary pressure, and therefore the pressure in the choroid plexus which largely determines the rate of formation of cerebrospinal fluid, may thus be proportional to the mean arterial pressure. Any final conclusion on this matter is, however, unwarranted until we have precise knowledge of the mechanism of hypertension.

SUMMARY

1 The general clinical features presented by hypertensive patients with cerebrospinal fluid pressures of 250 mm water and over contrast strongly with those presented by patients having lower pressures. The former are younger, the kidneys are usually severely damaged and the

* Shelburne, Blain and O'Hare (21) seem to have refrained from drawing a similar conclusion because they found that the cerebrospinal fluid pressure was unaffected by a rise of arterial pressure produced by brief compression of an arteriovenous aneurysm. This observation is not strictly relevant, because it is the effect of a persistent, and not of a brief, rise of arterial pressure that are considered here.

disease progresses rapidly to a fatal termination. The latter are older, the kidneys usually escape severe damage and the disease progresses less rapidly.

2 Every patient with a cerebrospinal fluid pressure over 250 mm water developed albuminuric retinitis. With one exception every patient with a lower cerebrospinal fluid pressure had either no retinal lesion or the lesions characterising arteriosclerotic retinitis. It is suggested that the essential difference between these two forms of retinitis is the addition in the albuminuric type of neuroretinal oedema resulting from increased intracranial pressure.

3 In individual patients with high blood pressure, the cerebrospinal fluid pressure has been found unaltered during headache and during acute attacks of coma and convulsions unassociated with uræmia.

4 There is a relation between high diastolic blood pressure and high cerebrospinal fluid pressure, and it is suggested that the former is one of the factors determining the latter.

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FURTHER OBSERVATIONS ON THE VESSELS AND NERVES OF
THE RABBIT'S EAR, WITH SPECIAL REFERENCE TO THE
EFFECTS OF DENERVATION *

BY R T GRANT

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THE observations described in the following paper were undertaken largely in the hope of obtaining further knowledge of similar phenomena occurring in man as a result of operative procedures for the relief of diseased conditions of the peripheral vessels. So far as is known, the vessels of the rabbit's ear correspond closely in their anatomy and physiology to those of the human extremities, and they offer the great advantage of being open to direct naked eye or microscopic examination in the intact animal. In man the state of the vessels has to be gauged, for the most part, indirectly by secondary phenomena, such as skin colour and temperature or by limb volume, in the rabbit, the vascular state can be observed directly and can be correlated with these secondary phenomena.

Some effects of denervation in the rabbit's ear have been described briefly in a previous paper (14), but since then more information has been obtained. Before going on to describe in detail the changes that take place in the vessels after removal of their nervous control, it is necessary to refer to the normal vasomotor reactions for, although the rabbit's ear has been used for many years in experiments, much of the recorded work is vitiated by insufficient physiological knowledge.

Methods

Choice of animals Throughout we have used albino rabbits for, although the larger vessels are easily observed in the coloured animals, the skin pigment obscures the ground colour of the ears, alterations of which are easily seen in albinos and which are important as indicating the state of the minute vessels.

* Work undertaken on behalf of the Medical Research Council

Many of our observations have been made on unanæsthetised animals and it is of help to choose an animal of a disposition suitable to the experiment in hand. Thus, to observe the vasomotor effects of body temperature it is best to have a stolid animal, one not easily disturbed by conversation or movements in the room, and which will sit quietly for long periods. On the other hand, the vasomotor effects of emotional disturbance are most clearly shown by a nervous animal, which remains on the alert and reacts vigorously to sensory stimulation.

Preparation of the ears The hairs may be removed either by clipping with scissors or by a barium paste. Care must be taken not to injure the skin and should this happen, as is shown by reddening, observation should be delayed until the reddening has subsided. It will be shown later (p. 6) that local injury to some extent modifies the vasomotor responses. Since reddening of the skin may not appear for several hours after the application of the barium paste, the ears should be prepared 24 to 48 hours beforehand.

Control of the animals The unanæsthetised rabbit will not sit still for long unless restrained. The restraint, however, need only be slight. In early observations we enclosed the body of the animal in a wooden box, the head being exposed, but we have since discarded this as unsatisfactory. Sooner or later the animal struggles and may injure itself. A satisfactory method of restraint is to cover the body of the sitting animal with a cloth, the ends of which are held down on each side by sandbags. Usually, if the rabbit is kept warm and has recently been fed, it will remain quiet and drowsy for long periods with only occasional movements. A cold or a hungry rabbit is apt to be restless, a rabbit will become restless if warmed too much. It is important to warm the animal artificially, for if it is inactive body temperature falls, we do this by placing the rabbit on a flat, cloth-covered copper box through which water circulates, warmed to the degree required for the particular observation.

Anæsthesia Whenever possible, we have used the unanæsthetised animal and certain reactions are obtainable only in this state. For certain purposes the quietude (not so much of the muscles, but of the nervous system), obtained in the way just described, is insufficient and light anæsthesia is necessary. We have found a 10% aqueous solution of sodium luminal satisfactory when injected subcutaneously in doses of 1.0 to 1.5 c.c. per kg. of body weight. The solution is best used freshly prepared, after several days a precipitate forms and the solution is less effective on injection. Within an hour of injection the animal, if kept warm and undisturbed, lies quietly asleep and will remain so for at least 6 hours. If it is cooled or warmed too much it will become restless, if it is handled carelessly or pinched it will struggle momentarily. The animal is again fully awake after 24 to 48 hours. The injection may be given repeatedly at intervals of about a week without obvious ill effects. Observations involving cutting the skin and dissection require the addition of either local novocaine or general ether anæsthesia according to the circumstances.

Blood pressure estimation The device which we have used for estimating the blood pressure has already been described elsewhere (15) The capsule is shown attached to the ear in Fig 7

Recording the state of the ear vessels In describing the ear vessels it is convenient to divide them into three groups We shall speak in the following pages of (a) the main vessels, meaning the central artery, its main branches and the chief veins, (b) the small vessels, meaning the network of small arteries and veins that cover the blade of the ear and are visible to the naked eye, of (c) the minute vessels, the term including the arterioles, venules, arteriovenous anastomosis and the capillaries, which are indistinguishable as separate vessels to the naked eye but give rise to the ground colour of the ear The state of the minute vessels is readily gauged by this ground colour

The thin blade of the ear rapidly dissipates heat and thus alterations of the bloodflow through it are quickly reflected in changes of temperature Provided that the room air is still and that the rabbit is quiet, the surface temperature of the ear is a good index of the state of the vessels The temperature is measured galvanometrically, constantan-copper thermal junctions being attached to the blade of the ear, as is shown in Fig 7 When the junctions are attached to comparable spots on the two ears their recorded temperatures are very close to each other, within 0.5°C , and under controlled conditions the same temperatures can be recorded from the ears day after day It is convenient to have the leads to the junctions interrupted by a small vulcanite plug and holder at the base of the ears The rabbit can then be turned loose without disturbing the junctions strapped on the ears All temperatures are given in the centigrade scale

Intravenous injections To avoid disturbing the head region, a cannula can be inserted conveniently into the small vein which runs up the back of the thigh, along the line of the sciatic nerve It lies subcutaneously embedded in the stout fascia covering the muscles

The arrangement of the rabbit for observation under luminal is shown in Fig 7

Normal control of vasomotor tone

Under ordinary conditions of laboratory examination it will be seen that, usually, the calibre of the ear vessels is constantly varying, the ears flushing and paling These changes occur irregularly and often very rapidly They are brought about through the varying activity of the sympathetic nerves and their activity is in turn controlled mainly by the body temperature and by the sensory nerves In general terms it may be said that when body temperature is low the vessels are narrowed, when high they are relaxed, relatively weak sensory stimuli cause constriction, relatively strong ones dilatation usually preceded by constriction The chief single factor controlling the calibre of the vessels is the body temperature, and it is only when the body is normally warm that the effects of sensory stimulation are conspicuous These general remarks

require amplification, and we will consider first the effects of body temperature

Effects of body temperature The effects of body temperature are most conveniently studied in the lightly anaesthetised animal, for then the responses to sensory stimuli are much reduced. We have not observed any material difference between the normal and lightly anaesthetised animal in the effects of body temperature on the ear vessels.

In a rabbit asleep under luminal and when precautions are taken to avoid disturbing it in any way, the vascular state of the ears is almost entirely controlled by the body temperature. Room temperature has but little effect on the vessels. When the rabbit is cold, that is when the rectal temperature is about 37°C or less, the ground colour of the ears is blanched, the smaller vessels are almost invisible while the main vessels are reduced to mere threads as is shown in Fig 9 (right ear). The temperature of the ears is little if at all above that of the room. It is of interest to note that though the bloodflow to the ears is greatly reduced in the cold animal, it is not entirely brought to a standstill. This can be shown easily by examining the ear microscopically or by stripping the central artery with the fingers distally, when the blood will be seen slowly to fill the artery from below upwards. The portion of the artery pressed on by the fingers dilates and remains dilated for a considerable time (see a previous paper (13)).

If the central artery of the blanched ear is watched closely, it will be seen that, every now and again, a wave of slight relaxation passes slowly up the artery. It may appear in several parts of the artery and not simultaneously in different parts. The mechanism of these small movements is unknown, they may be due to slight alterations of sympathetic tone, they resemble the oscillations in calibre previously described (13) in vessels both normal and denervated under the influence of adrenaline or histamine.

If now the animal is slowly warmed up, the state of the vessels changes but little until the rectal temperature has risen to about 38.5° . As the rectal temperature approaches and passes this level, the central artery relaxes at first slowly, then rapidly and again slowly, the smaller vessels follow suit and the ear becomes flushed (Fig 8, right ear). These changes occur simultaneously in both ears and their temperatures rise in an S-shaped curve, at first departing slowly from room temperature then quickly and finally, as rectal temperature continues to rise, coming to be about 2°C below rectal temperature. Further body warming causes no appreciably greater dilatation of the vessels, they remain steady in calibre and the ear temperature runs parallel to and about 2°C below rectal temperature. It has been pointed out by Krogh (22) and by Grant and Bland (11) that at this upper range of body temperature, although the main and small vessels are fully relaxed, the minute vessels, though dilated, are not maximally so. In the following pages, when we speak

of the ear vessels as being fully relaxed by body warmth, this qualification must be borne in mind. The flush of the ground tone can be deepened considerably in several ways, by local heat, faradism, mechanical stimulation, by reactive hyperæmia, various drugs and by antidromic sensory nerve stimulation. The deepening of the ground tone produced by antidromic stimulation is shown in Fig 11 (left ear). When a hot animal is cooled, the vessels constrict in the reverse order, paling of the ground tone occurs first and constriction of the main vessels last. The fall of ear temperature when a hot animal is slowly cooled is exemplified in Fig 1 (right ear).

Although we have mentioned 38.5° as the rectal temperature at which the calibre of the vessels changes from constriction to dilatation or the reverse, according to whether the body is being warmed or cooled, we give that temperature only as an indication, it varies considerably not only in different animals but also in the same animal from time to time. It is true to say that there is an upper level of rectal temperature, usually about 39° , above which the vessels are fully and steadily relaxed, the animal is then in what we have previously termed the "hot state" (14). It is true also that there is a lower level, usually about 38° , below which the vessels are greatly constricted, the animal being in the "cold state". Sometimes, however, the ear vessels are fully relaxed when rectal temperature is as low as 38° while on the other hand, full relaxation may not be attained until rectal temperature has risen to 40° or over. We have not so far determined the factors responsible for these variations but we have found that in individual rabbits anaesthesia tends to lower, while operative procedures or periods of ill health raise, the level of body temperature at which the ears become flushed. In the intermediate or "reactive" state, when the animal is neither hot nor cold, the vessels are unsteady in calibre, constricting or dilating according to whether the rectal temperature is falling or rising. Whether or not they would remain steady in calibre if rectal temperature could be maintained exactly constant at any one point in this intermediate range we do not know. We have not been able readily to keep rectal temperature exactly constant and it has not been necessary for our purpose. Another factor which interferes with the analysis of the relation of body temperature to vascular tone is that in this reactive state, and even when the rabbit is under luminal, the vessels seem to be unstable, and any sensory stimulus to the animal, such as a slight draught of air, or a small movement on the part of the animal itself, will cause a rapid and often considerable, though temporary change of calibre, usually in the direction of constriction. Even when precautions are taken to screen the animal from draughts, to cover the eyes and keep the room quiet, apparently spontaneous changes are apt to take place in the calibre of the vessels independent of the rectal temperature. These changes are the less liable to occur the deeper the anaesthesia. They are conspicuous in the unanaesthetised animal. So it happens that when the animal is neither hot nor cold

and an attempt is made to maintain the rectal temperature within the range of a few tenths of a degree, the calibre of the ear vessels and the ear temperature are continually fluctuating. So also when a rabbit is warmed or cooled slowly, the vessels do not usually pass smoothly from either full dilatation or constriction to full constriction or dilatation but undergo one or more fluctuations as body temperature passes through the intermediate range. In either the hot or cold state, the vessels remain steadily dilated or constricted (except for the minor oscillations already noted in the cold state).

Effects of sensory stimuli. We have now to consider the effects of sensory stimuli on the vessels, body temperature being controlled. These are best studied in the unanaesthetised rabbit. We have said previously that relatively weak sensory stimuli cause constriction and relatively strong ones dilatation. Thus for example, a hand clapped on the rabbit's back causes the ear vessels to constrict, piercing the skin with a hypodermic needle also causes constriction, often followed by dilatation. Dipping the hind foot into cold water constricts the ear vessels, but if the water is ice cold, the constriction is followed by dilatation. The effect of any stimulus, however, is modified to a certain extent by the rectal temperature. These reflex effects are best seen in the intermediate range of body temperature, when the animal is neither hot nor cold. If the vessels are already well constricted by low rectal temperature, sensory stimulation produces no obvious further constriction, and, the colder the animal, the more difficult it is to produce vasodilatation by stronger stimulation. Also, if the rectal temperature is high and the vessels already fully dilated, mild stimuli produce no appreciable vascular effect, strong stimuli may cause a slight and evanescent constriction but the vessels do not subsequently relax beyond their original state. The higher the rectal temperature, the more difficult it is to produce a reflex vasomotor effect. We have also mentioned earlier that injury to the ears modifies to some extent their vascular reactions. If one ear is in part injured, for example by scratching or by burning with barium paste, dilatation seems to be more readily provoked in that ear as a whole. Thus when the body is warmed this ear flushes first and at a lower body temperature than the other ear, it lags behind the other ear when constriction is produced by cooling the body, also, dilator reflex responses to sensory stimulations are more easily elicited in the injured ear.

These then are the chief factors normally controlling the state of the ear vessels and we may now pass on to consider the effects of nerve section.

It may be remarked in passing that these vasomotor reactions in the rabbit are very much the same as in man. In man the vessels respond similarly to body temperature. Anyone who has recorded limb volume in man knows the difficulty of obtaining either a steady base line, or

equal responses from apparently equal sensory stimuli. The base line is unsteady when the subject is normally warm, it becomes steady if the subject is either hot or cold, but in these states the vasomotor responses to stimuli tend to be reduced. A point of difference, and an important one, is that in man the spinal reflex response to sensory stimulation seems to be constrictor only, we have not seen dilator effects to correspond with those in the rabbit.

Vascular effects of denervation

Goltz (12) first showed that after cutting vasomotor nerves in dogs, a state of moderate vascular tone remains, this tone later increases and becomes more equal to the original one. This observation has been repeatedly confirmed. Dale and Richards (9) showed that the vessels of the cat's limb to which the nerves have been cut, after an initial loss of tone, rapidly acquire a new one. They further showed that the denervated vessels acquire an increased sensitivity towards adrenaline and other drugs. Grant and Bland (14) have noted the regain of tone in the vessels of the rabbit's ear after section of the nerves.

To study the immediate effects of completely interrupting the sympathetic nerves to the ear vessels, it is sufficient to cut the cervical sympathetic cord and the vertebral ramus, an operation, which, as Dr. Feldberg showed me, is easily performed from the front of the neck. To prevent regeneration and so study the remote effects of nerve section, it is necessary to excise both the superior and the stellate sympathetic ganglia.

Immediate effects Immediately, and for some time, after cutting the sympathetic nerves or excising the ganglia, the vessels of the ear are widely dilated. They no longer respond reflexly to sensory stimulation or to changes of body temperature. The ear temperature, no matter whether the animal is hot or cold, lies about 2°C below rectal temperature, and its vessels remain steady in calibre whether the rabbit is active or at rest, nervous or quiet. The loss of tone in the denervated vessels, however, is no more or no less than that in the vessels of the normal ear when the animal is hot, the denervated cannot then be distinguished by inspection from the normal ear and their temperatures are equal (Fig. 8). In both, the main vessels and the smaller vessels seem to be fully dilated, the minute vessels are only partly dilated, the equally pink ground tone of the ears can be flushed much more in the ways already described. Moreover, the freshly denervated vessels are no more sensitive to the action of various drugs than are those of the normal ear, the vessels of the normal ear being dilated by raising the body temperature. We have tested repeatedly the effects of injecting intravenously adrenaline, histamine and pituitrin without detecting any difference in the vascular reactions of the two ears under these conditions. The effects described above are a constant result of sympathetic nerve section and we have

demonstrated them to other workers in the laboratory. They are seen in both the normal rabbit and the rabbit asleep under luminal. It may be remarked here that so far as we know, there is no evidence for dilator fibres in the sympathetic nerves to the ear, and the dilatation resulting from body warming or reflexly from sensory stimulation is regarded as due entirely to the inhibition of constrictor fibres. Recently, however, Burn (3) has produced evidence for the presence of dilator fibres in the peripheral sympathetic nerves of the dog and Lewis and Pickering (27) for their existence in man. The observations described above indicate that, if there are dilator fibres in the sympathetic nerves to the rabbit's ear, they can play but a small part in causing dilatation and that this must be due almost entirely to the inhibition of constrictor action. For, it would be thought that if the dilatation from body warming, for example, is due not only to inhibition of constrictor, but also to the stimulation of dilator fibres then section of the sympathetic nerves should result in a dilatation less in degree than that due to body warming. We have seen however that there is no appreciable difference in the degree of dilatation produced in the two ways. Lewis and Pickering similarly failed to obtain decisive evidence for dilator fibres in the cat's ear (27).

Later effects. The vessels of the denervated ear do not long remain in their greatly dilated state, within a few hours they begin to show a regain of tone. This continues for about 5 to 7 days, after which time no further change takes place. We shall consider now the state of the vessels after tone has been regained fully and return later to the question of its onset and development (see p. 15).

In the first place, to say that the vessels regain tone does not express fully the changes that take place. It is true that the vessels become less dilated than they were immediately after operation, but this is not all. The most striking thing is that the vessels regain reactivity and show great variations in tone. At one time they may be greatly dilated, almost as much as when the nerves were freshly cut, at another, they may be greatly constricted like those of the normal ear when the rabbit is cold. In general, the denervated vessels come to react much like those of the normal ear and react similarly to similar stimuli, though the changes of calibre happen more slowly than, and are not usually so great as, those of the normal vessels. We have satisfied ourselves that this regain of activity is due neither to incomplete removal of the sympathetic nerves nor to rapid regeneration. Section of all the remaining (sensory) nerves makes no difference to this reactivity, while post mortem dissection and histological examination fail to reveal any connection of the nerves with the vessels. Although there is a general parallelism between the reactions of the two ears, the relationship is not a strict one, by suitably altering the conditions under which the animal is observed, one ear, either the normal or the denervated, may be rendered pale while the other is flushed. The chief factor controlling the denervated vessels

seems to be activity of the animal, either muscular or nervous, activity tending to cause constriction, quiescence relaxation. The parallelism between the reactions of the two ears happens because activity also stimulates the sympathetic nerves to the normal ear. The differences between the reactions arise because body temperature, which is a chief controlling factor on the normal, has no appreciable effect on the denervated vessels except in so far as cold or warmth modifies activity.

The independence of the tone of the denervated vessels on *body temperature* is most readily displayed in the rabbit asleep under luminal. Then, no matter whether body temperature is high or low, the denervated

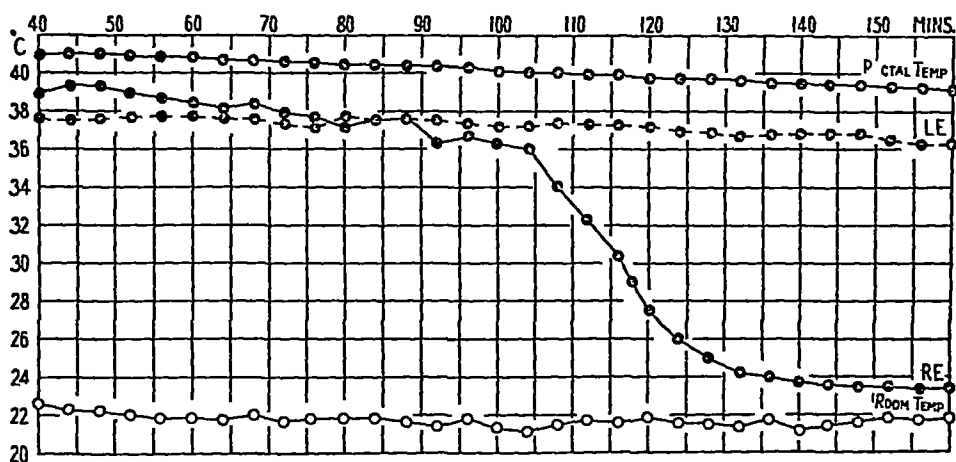


Fig 1 Rabbit HN, 20/7/31, under luminal, 4 months after removal of left superior cervical and stellate ganglia. The rabbit, after being warmed was cooled slowly. The chart shows temperatures of the ears, rectum and room during the cooling. The right normal ear is at first more flushed and warmer than the left, its temperature rides about 2° below rectal temperature. It diverges from this slowly from the 50th to the 105th min, rectal temperature having fallen a little more than 1° to 40° . During the next 25 mins, the right ear becomes pale and cool and its vessels greatly constricted, thereafter its temperature approaches that of the room. The temperature of the left sympathectomised ear remains parallel to, and about 3° below that of the rectum, its vessels remain unchanged throughout.

ear is flushed, its vessels are dilated and its temperature lies 3 to 4° below rectal temperature, the state of the normal vessels depends on the body temperature as already described. When this is sufficiently high to produce the maximum relaxation of the normal vessels obtainable in this way, it will be seen that those of the denervated ear are almost, but not quite, as dilated (Fig 10, left ear). The ground colour of the denervated ear is slightly but definitely paler, and the small vessels are less in evidence, the main vessels are little if at all narrower than the normal ones. We have already pointed out that the vessels of a freshly denervated ear are in the same state as those of a normal one when the animal is hot, so that the comparison of the two ears in the

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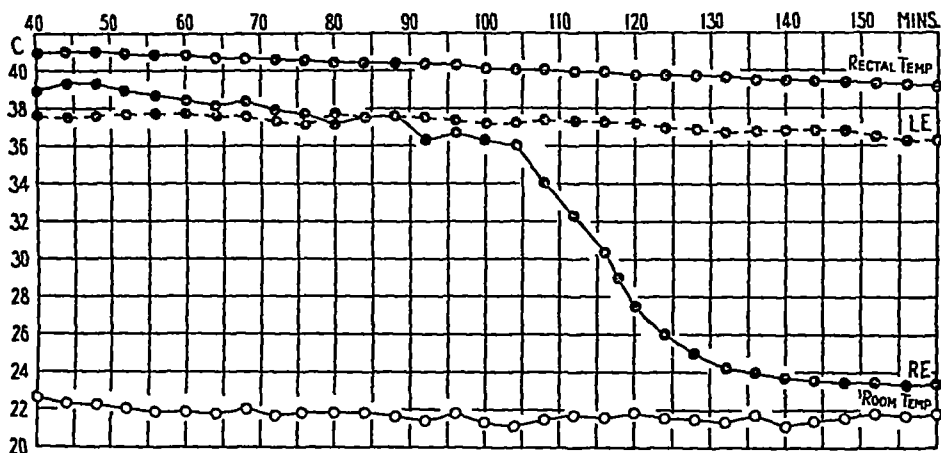


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present case shows how little the regain of tone is, we shall return to this point later (p 14). To continue when body temperature is lowered, the normal vessels constrict and normal ear temperature falls to that of the room. The denervated ear remains unchanged in appearance and its temperature continues parallel to rectal temperature (Fig 1). The same things can be shown in the unanaesthetised rabbit, provided that a suitable animal is chosen. Thus, if we take a rabbit of placid disposition and well used to handling, and which has been moving about for some time in a cool room, it will be found that the ear vessels are constricted. Both ears are equally pale and cold, and the visible vessels of the denervated side are little if at all larger than the normal ones. If now the rabbit is placed on the unheated copper bath, then, provided that

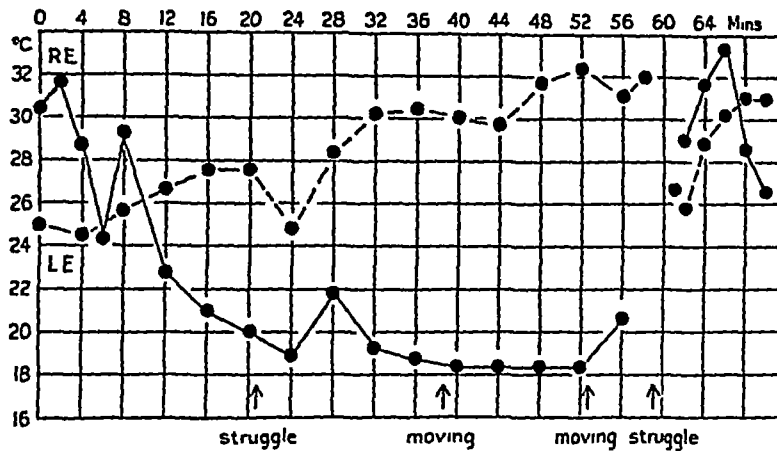


Fig 2 Rabbit MN, 24/10/33, 15 days after removal of left superior cervical and stellate ganglia. Rabbit observed on copper bath, unwarmed. The chart records ear temperature. The animal sat quietly except at the times indicated on the chart. The left ear vessels, at first constricted, slowly relaxed, relaxation was interrupted and replaced temporarily by constriction when the animal moved, ear temperature falling. The right ear vessels varied in calibre as shown by the fluctuations of temperature. At 58 min the rabbit was placed on the floor, held by one hind leg so that it struggled and was then quickly replaced on the bath. Both ears were then pale. The right ear quickly flushed and then paled again. The left ear vessels constricted further for 2 min then relaxed and remained so.

it sits quietly and is undisturbed, the denervated vessels slowly relax while the normal ones remain constricted. When the animal is warmed, the normal vessels also relax and ultimately become a little more relaxed than those of the denervated ear. Cooling again narrows the normal vessels, but leaves the denervated ones unchanged.

It is clear from these observations that the tone of the denervated vessels is independent of the body temperature. A point of some importance is that the denervated vessels do not relax smoothly. Relaxation takes place by a series of oscillations, the vessels relax slightly then constrict again a little, they relax a little more and again constrict a little, and

so on until relaxation is complete when the oscillations cease. The significance of these oscillations is discussed later (p. 14).

We come now to the effects of *nervous and muscular activity* on the denervated vessels. If in the experiment just described on the unanæsthetized animal, the rabbit moves after the denervated vessels have begun to relax, then relaxation ceases and they constrict. They constrict to a less degree and more slowly than the normal ones. When the rabbit once more becomes quiet, the denervated vessels, after a pause, once more begin to relax. The same thing happens if a quiet animal is startled. Moreover, if the animal chosen for the experiment is nervous, the denervated vessels remain constricted (Fig. 4, p. 18) unless and until the rabbit settles down to rest quietly, when they relax slowly. The degree of relaxation obtained depends on how quiet the animal is. Sometimes the vessels dilate but slightly and it is only in an animal that itself relaxes and becomes drowsy that the denervated vessels dilate to the same degree as they do when the rabbit is under the influence of luminal. Even under luminal, sensory stimulation, by repeatedly pinching or pricking the skin, will cause constriction of the denervated vessels which is the greater the more the animal struggles. These observations are exemplified in Fig. 2.

DISCUSSION

In a previous paper (14) it was remarked that it seemed possible that the smaller calibre of the denervated vessels during bodily activity and after fright might be due to the release of adrenaline, which is believed to occur under these conditions, and that the loss of tone when the animal is at rest or under luminal might be due to a decrease in the amount of circulating adrenaline. These remarks were applied to the totally denervated ear, but as regards regain of tone and the phenomena associated with it, the vessels deprived of all their nerves do not differ from those deprived of their sympathetic supply alone. In two rabbits we excised the sympathetic ganglia on one side and at the same time totally denervated the other ear. In both rabbits the vessels of the two ears behaved alike subsequently. Dale and Richards (9) have shown that the denervated vessels of the cat's limb acquire an increased responsiveness to chemical stimuli of all kinds and they suggested that the regain of tone might be accounted for by this increased responsiveness to adrenaline. They discarded this suggestion on the ground that in the cat small doses of adrenaline produce not constriction but dilatation. More recently Dale (8) has remarked that while formerly of tone in denervated vessels might be attributed to the vasomotor hormones in previously ineffective concentrations, experiments seem to have cut us off from recourse to this explanation. We shall return to this point later. Now as we have not been able to find that adrenaline has any action

a constrictor one on the ear vessels, and it seems to us that the phenomena described in the foregoing pages could be accounted for entirely by an adrenaline-like substance circulating in the blood stream, together with an increased sensitivity of the denervated vessels to its action. Further observation has shown that, as in the cat's limb, so in the rabbit's ear, the denervated vessels become more responsive to various stimuli.

Increased responsiveness of denervated vessels To compare the responsiveness of the normal and denervated ears to various stimuli, it is necessary to have the vessels as far as possible in a stable condition and of equal calibre on the two sides. We have therefore not tested the effects of dilator stimuli, since it is only when the animal is at rest and warm that these conditions are satisfied, and in this state the vessels of both ears are already almost fully dilated. We have tested repeatedly the effects of adrenaline, pituitrin, histamine and ergotoxine* on the unanaesthetised rabbit by subcutaneous injection and in the rabbit under luminal by intravenous injection. To all these substances and in the normal and the anaesthetised rabbit the denervated vessels respond much more strongly than the normal ones. With suitable dosage the denervated vessels can be considerably constricted while there is no appreciable change on the normal side. These substances produce effects equal in the two ears before and immediately after nerve section, the increased effect on the denervated side is only fully displayed after tone has been regained fully.

The following observations exemplify the increased responsiveness of the denervated vessels in a rabbit under luminal and after tone has been fully regained. The intravenous injection of 0.0001 mg of adrenaline had no appreciable effect on the normal vessels but, in the denervated ear, caused paling of the ground tone and slight but definite constriction of the smaller and the main vessels, the whole effect lasting about two minutes. The injection of 0.001 mg adrenaline produced only a slight paling of the ground tone of the normal ear, but great paling of the ground tone, great constriction of the small vessels and moderate constriction of the main vessels on the denervated side, the whole effect lasting about four minutes. When histamine is injected, the minute vessels dilate while the arteries contract. In the same rabbit the injection of 0.001 mg neutralised histamine acid phosphate produced flushing of the ground tone but no appreciable effect on the visible vessels of the normal side. On the denervated side, however, it caused not only flushing of the ground tone but also slight narrowing of the visible vessels. The injection of 0.01 mg produced a correspondingly greater effect on both sides. The difference in the response of the two ears is as striking in the case of both pituitrin and ergotoxine.

* According to Dale (7) ergot has no constrictor effect on the rabbit's vessels. We find that both liquid extract of ergot and ergotoxine strongly constrict the vessels of both the normal and the denervated ear, these observations, undertaken from a different point of view, will be reported elsewhere.

The denervated vessels are more responsive not only to chemical stimuli, but they also react more strongly to other forms of stimulation. Thus local faradisation of the central artery produces a more intense and longer lasting constriction on the denervated side. Again, when the ears are immersed in cold water or when a draught of air is blown across them, the constriction of the denervated vessels is obviously the greater and the longer lasting. It is to be remembered in all these observations, that the rectal temperature must be maintained sufficiently high to inhibit the sympathetic nerves, otherwise the normal vessels may respond vigorously.

It seems clear, then, that the denervated vessels of the rabbit's ear acquire greatly enhanced responsiveness to constrictor stimuli of various kinds. Dale and Richards (9) take this enhancement to mean that the reactivity of the normally innervated vessels is restricted by the effect of tonic impulses from the nerve centres, only when these are cut off, and when the stimuli aroused by nerve section and by the processes of degeneration have passed off, can the contractile elements exhibit their unhampered response to these drugs. We shall return to this point at a later stage (p 19), and we may now consider the question of a possible dilator effect of adrenaline in minute doses.

Effect of adrenaline in minute doses So far as we know, the only evidence for dilatation produced by adrenaline in the rabbit's ear is that of the Meltzers (29). They observed a preliminary constriction followed by dilatation of the ear vessels when small doses of adrenaline were injected into the ear vein. It seems to us, however, that the vascular reactions observed by them are the usual ones to expect from the stimulus of injection. We have pointed out that dilatation preceded by constriction is the usual result of relatively strong sensory stimuli and when care is taken to avoid sensory stimulation during injection, adrenaline does not cause dilatation. We have repeatedly observed the effects of small doses of adrenaline in both normal and denervated ears in all states of vascular tone, and the minimum effective doses have caused only constriction and never dilatation. This is in agreement with Flatau (10) and with Clark (6) who found that even in the cat, the smallest effective amount of adrenaline always produces a diminished flow of blood through the skin. We may add also, in the rabbit's ear, we have failed to reverse the constrictor effect of adrenaline by ergotoxine.

of tone, for we have seen that under suitable conditions of quietude and muscular relaxation the tone of the long denervated vessels may be almost as low as it is immediately after nerve section. We may note here that the oscillations of the main vessels as these relax after being constricted can readily be interpreted as due to a diminishing concentration of the adrenaline-like substance. Similar oscillations are seen in the arteries after the local application of adrenaline and other constrictor substances as is described in an earlier paper (13, *see also* 14). Two points, however, remain for further discussion. We have noted that the vessels of the denervated ear are abnormally sensitive not only to chemical stimuli but also to the application of cold, it may be that they are likewise abnormally sensitive to changes of blood pressure. We must therefore inquire what part these factors play in the reactions of the denervated vessels, for when the rabbit struggles or moves it moves its ears through the air and activity is associated with changes of blood pressure. That the reactions of the denervated vessels are mainly independent of both these factors is clearly shown by the following observation which we have made repeatedly.

A rabbit, with one ear denervated at least a week before, is placed on the copper bath, warmed and left undisturbed until the vessels are fully relaxed. The blood pressure is estimated in the normal central artery. The rabbit is next placed on the floor and held by one hind leg so that it struggles, for a half or one minute. It is then quickly replaced on the bath and blood pressure is estimated at intervals. When the rabbit struggles, the normal vessels constrict at once and relax again as soon as the movements cease. The denervated vessels constrict more slowly, they go on constricting for a short time after the struggling ends and then, as the animal settles down quietly, slowly relax. Blood pressure is found to be raised by 10 or 15 mm Hg at the end of the struggle, it returns gradually to its previous level as the denervated vessels relax. In our early observations in which the rabbit was confined in a wooden box, we frequently noted a momentary flushing of the denervated ear as the animal began to struggle in the box, the flush being presumably due to a sudden rise of blood pressure. This flush, however, was quickly replaced by pallor as struggling continued. Moreover, we find that the blood pressure of a rabbit resting quietly and with the denervated vessels relaxed, is about 10 mm Hg lower than when the animal is on the alert and nervous with the denervated vessels constricted. Again, when the observation just described is repeated with the ears covered in cotton wool during the struggle, to prevent them being cooled by movement through the air, the subsequent vascular reactions are unaltered. But, while it is clear that alterations of blood pressure or movement of the ears through the air are not in the main responsible for the alterations of the tone of the denervated vessels, yet the tone is affected to some extent by the temperature of the surrounding air. For example, when

a rabbit is put to rest with the denervated vessels constricted, they relax more readily in a warm than in a cold room. Also, if the denervated vessels have been strongly constricted for some time and ear temperature has fallen to that of the room, then when the rabbit becomes quiet, relaxation may be long delayed. It can be hastened by warming the ears, for example, by laying them along the animal's back, and when the ears are re-exposed the denervated vessels remain relaxed (Fig 3)

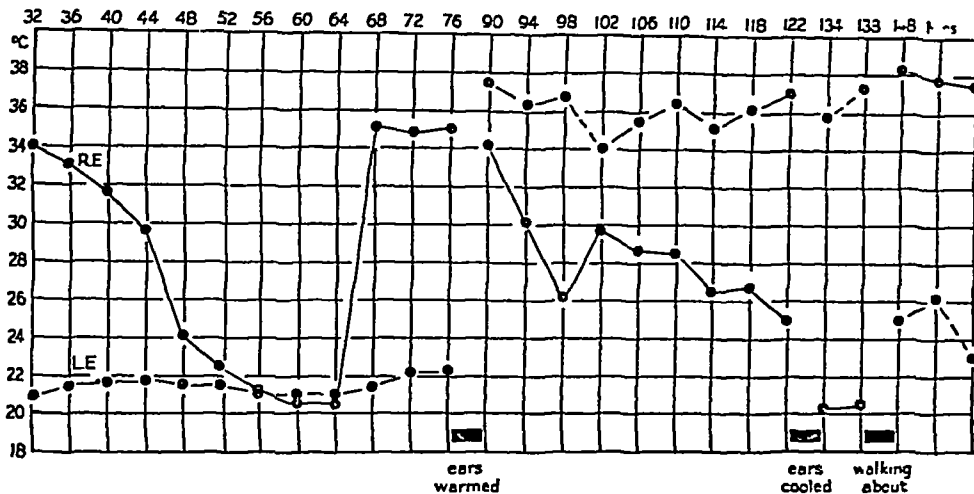


Fig 3 Rabbit HN, 4/4/32 9 months after sympathetic denervation of left ear. The rabbit had been moving about the room (temperature 18.5°) for half an hour. Vessels of right normal ear varying in calibre, those of the left denervated ear greatly constricted. Animal observed on the copper bath unwarmed. It sat quietly moving only occasionally. The ear temperatures are recorded in the chart. The vessels of the right ear continued to vary in calibre ear temperature fluctuating. The left ear vessels remained constricted and its temperature low. Between 76 and 90 min the ears were warmed by laying them along the animal's back under the cloth covering. On re-exposure the left ear remained warm and its vessels dilated. Between 122 and 134 min, room temperature having risen to 26° the ears were exposed to a draught of a fan. When the fan was stopped both ears were pale and cold. The right ear remained so the left ear soon reflushed and remained so. Between 138 and 148 min, the rabbit was allowed to run about the room and was then replaced on the copper bath. The right ear had become flushed the left pale and cold. The ears remained unchanged until the end of the observation at 157 min.

stated that a slight paling of the ground tone (as compared with that of the fully flushed normal ear) can be recognised two hours after nerve section, while after 18 hours the ground tone is definitely paler and the larger vessels are reduced in size. Further observation has shown that the earliest time at which the regain of tone can be recognised depends on the state of the animal after operation, the regain is displayed sooner in an active than in a quiet rabbit. Thus, if the operation is done under open ether only and the rabbit recovers quickly and moves about, then the regain of tone can be seen in about two hours as a just perceptible paling of the ground tone of the denervated as compared with the normal ear when this is fully flushed. On the other hand, if the animal is in addition under the influence of luminal and remains sleeping quietly after the operation, then the regain of tone is inappreciable till considerably later. How much later, depends on the state of the normal ear. If the normal ear is kept flushed continuously by body warming (and not only flushed at intervals to compare it with the denervated ear) it, too, may show a slight increase of tone which interferes with the recognition of the early stages of its onset in the denervated ear. The denervated ear, however, regains tone faster than the normal and the difference between the two can be recognised clearly about 24 hours after operation. Now, although in the rabbit under luminal the regain of tone appears to be delayed, yet an early increased responsiveness of the vessels to adrenaline can be recognised. For example, in one rabbit under luminal there was no appreciable difference in the appearance of the normal and denervated ears about five hours after operation but the denervated vessels responded more strongly to the intravenous injection of adrenaline. The meaning of the apparent variation in the time of the earliest recognisable regain of tone now seems clear. The tone of the denervated vessels depends on the concentration of the constrictor substance in the blood and on the responsiveness of the vessels to its action, which increases gradually after nerve section. So that the denervated vessels will acquire sufficient tone to be recognisably more constricted than those of the normal flushed ear earlier in an active (more substance, less responsive vessels) than in a quiet rabbit (less substance, more responsive vessels).

The responsiveness of the denervated vessels continues to increase for about a week. We have demonstrated this repeatedly by denervating first one and later the other ear. The difference between the two ears, at first striking, gradually lessens and disappears after five to seven days. After this time, no further increase takes place as a general rule. In our previous paper we said that we suspected that there is a further and gradual increase of tone so that the denervated ear tends ultimately to become pale and cool, remaining so even when the animal is at rest or under luminal. Further observation has shown, however, that this occurs only exceptionally, we have seen it in but one rabbit that remained in good health. The left superior cervical and stellate ganglia were excised from

this rabbit in March, 1931, and until after April, 1932, the vessels of the left ear showed the usual phenomena associated with denervation. The rabbit was not examined again until September, 1932. It was then found that the denervated vessels remained greatly constricted. They would relax when the ear was warmed but quickly narrowed again when the ears were re-exposed to room air. It was finally examined under luminal on 26/9/32 and again the denervated vessels remained constricted. The rabbit did not recover from the luminal and was found dead in the morning of 28/9/32. Nothing unusual was found at autopsy and microscopic examination of the ear vessels showed no difference between those of the two ears. We have watched at least three other rabbits for periods longer than six months after denervation (9, 13 and 15 months), but in these no further change took place in the vascular reactions after the first week. We have, however, occasionally seen a denervated ear become priler than we should expect and in which the vessels relaxed but slightly or not at all under the appropriate conditions. We have seen this after operations from which the animal did not recover completely for a day or two, we have seen it also with periods of ill-health, such as diarrhoea. It is significant that in these conditions the normal vessels are also affected, the level of rectal temperature at which the normal vessels relax is raised and when full relaxation is obtained the ground tone remains priler than usual. The observations seem to point to unusually high concentration of the adrenaline-like substance in the circulating blood, this leading to unusually high tone in the normal and denervated vessels, and tending to interfere with the relaxation of the normal vessels in response to sympathetic inhibition. A similar increase of vascular tone and rise in the level of rectal temperature necessary to flush the normal ear can be brought about by injecting adrenaline subcutaneously. Our observations on these points are not complete and we will not pursue them further here, we may say, however, that they suggest that this adrenaline like substance plays some part in maintaining normal vascular tone and in regulating body temperature.

We are left now with two main problems to discuss, namely, what is the source of the adrenaline like substance and what is the nature of the increased responsiveness of the denervated vessels. We shall consider each in turn.

The source of the adrenaline-like substance

We have not yet been able to trace the source of this substance, our observations show, however, that it comes neither from the suprarenal glands nor the pituitary body. In five rabbits we have excised the superior cervical and stellate ganglia on one side and, after vascular reactivity had been fully established, we have removed first one and, a week later, the other adrenal. These animals all recovered quickly and well from the operations, two died, one on the sixth, the other on the seventh day,

the others were killed on the 2nd, 3rd and 28th days after removing the second adrenal. In none of them was any change seen in the reactions of either the normal or denervated ear vessels (Figs 4 and 5). Dr Oliver Cope, of Boston, U S A, who was then working at the National Institute for Medical Research, very kindly helped us by removing the intrasellar

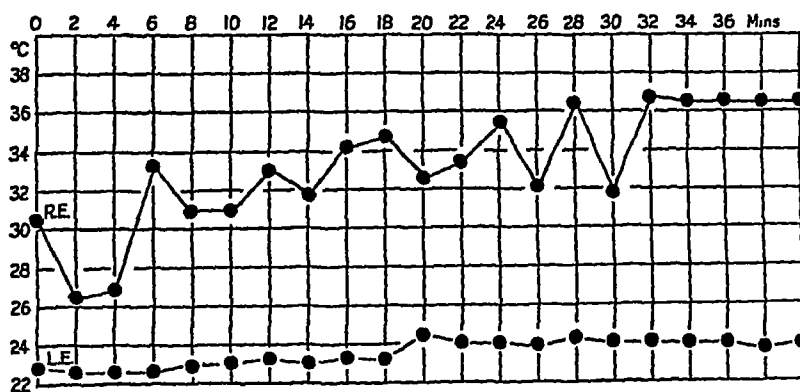


Fig 4 Rabbit MO, 31/10/33, 27 days after removal of left superior cervical and stellate ganglia, 7 days after excision of right, and 1 day after excision of the left adrenal. The animal has recovered well. Observed on copper bath and warmed, it remained scared and rather restless throughout the observation. Ear temperatures are recorded in the chart. The right normal ear flushed and paled repeatedly until the rabbit was sufficiently warm when it remained steadily flushed. The left denervated ear remained pale and cold throughout.

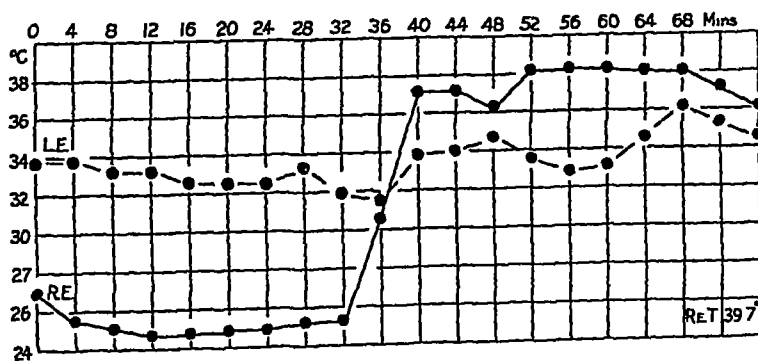


Fig 5 Rabbit MO, 6/11/33, 6 days after the observation summarised in Fig 4. The reactions of the denervated vessels are unchanged. The rabbit remains well but scared and restless, given a small dose of luminal to quieten it, 45 mins before the observation recorded in Fig 5. The animal now quiet, moving only occasionally, observed on the copper bath and warmed. The vessels of the left ear are well relaxed and the ear is warm. The right ear, at first pale and cold, becomes more flushed and warmer than the left.

pituitary body from eight rabbits and we are grateful to him for his assistance. Four of these recovered well and survived sufficiently long for good observations to be made on the ears. Two survived for 3, one for 15 days, and one for a month. In none of these four rabbits could we

detect any alteration in either the normal or the denervated ears. In the rabbit which survived for a month, we were able also to excise both adrenals and it lived for 7 days after the removal of the second gland. Again, we could detect no change in the vessels. All these animals were examined after death. In those in which the adrenals had been removed no trace of the glands or of accessory bodies was found. In all those in which the intrasellar pituitary body was excised, this was found to be entirely wanting. Further, a block of tissue was removed from the base of the brain in each one and examined in serial sections, a minute remnant of pituitary tissue was found attached to the base of the brain only in the rabbit which lived the month. These observations seem to exclude definitely the adrenals and the pituitary body as the source of the unknown substance.

Another possibility is that the unknown vasoconstrictor substance may be sympathin which, according to Cannon and his associates (5), is liberated into the blood stream from smooth muscle when this is stimulated through the sympathetic nerves. This, however, seems unlikely for, as Cannon and Bacq (5) and Butler and Garrey (4) found, vascular tone is regained and maintained in animals after complete sympathectomy. Butler and Garrey (4) note they were unable to obtain a free flow of blood from skin punctures in sympathectomised dogs and that in one dog the ears were pale and cool and that these did not redden or become warm even after exercise sufficient to produce severe panting as is the case in normal dogs. Other possible sources of vasoconstrictor substances are mentioned by Dale (8) but as we have no evidence to bring forward we may leave this point without further discussion.

The nature of increased responsiveness

Let us first turn to the view expressed by Dale and Richards (9), based on their observations on the cat's limb, that this enhancement means that the reactivity of normally innervated vessels is restricted by the effect of tonic impulses from the nerve centres, only when these are cut off and when the stimuli aroused by nerve section and by the processes of degeneration have passed off, can the contractile elements exhibit their unhampered responses to various stimuli. Now, in the present case, we need consider only the sympathetic nerves, since we have seen that the sensory nerves play no part in the development of the increased responsiveness. The recent work of Adrian (1) shows that, except in sensory nerves, and in them only for a short time, no stimuli can be detected electrically in the peripheral portions of cut nerves, we can therefore put aside stimuli aroused by nerve section. It is possible however that vaso-active substances might be released from degenerating nerve fibres, the gradual development of enhanced responsiveness over a period of days suggests that it is in some way associated with the processes of degeneration. To test this point, we have in five rabbits cut

the thoracic sympathetic cord centrally to the stellate ganglion and compared the vascular changes in the corresponding ear with those in the other ear, before and after extirpating the ganglia. Section of the thoracic sympathetic cord is easily accomplished by excising a portion of the second rib near the spinal column and opening the pleura, the cord is then found embedded in fatty tissue immediately beneath the wound. The results have been the same in all five rabbits. Immediately after preganglionic section, the ear vessels are fully relaxed like those of a normal ear when the rabbit is hot or when the ganglia are excised. As in the last case, they no longer respond to changes of body temperature. They also in the course of 5 to 7 days acquire an enhanced responsiveness. This, however, is not so great as when the ganglia are removed (Fig 6),

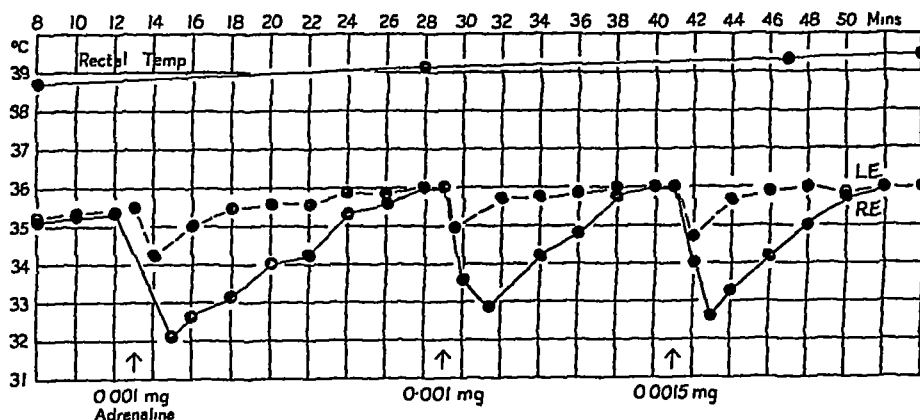


Fig 6 Rabbit OG, 26/9/34, under luminal, 3 months after removal of right superior cervical and stellate ganglia and section of left thoracic sympathetic cord below stellate ganglion. Rabbit observed on the copper bath. Chart shows the effect on ear temperature of 3 intravenous injections of adrenaline. The right ear vessels react more strongly than those of the left and temperature falls lower.

the vessels respond more vigorously than normally innervated vessels but less vigorously than vessels entirely deprived of their sympathetic nerves. That the postganglionic fibres remain intact is shown by stimulating the sympathetic nerves faradically, when the ear vessels constrict strongly. Assuming the correctness of the generally accepted view that all nerve fibres in the cervical sympathetic have cell stations in either the stellate or the superior cervical ganglion, a view which is based on the assumption that all the fibres are constrictor in nature, then the above observations seem to show clearly that enhanced responsiveness is not the result of nerve degeneration. If we are to believe that the increased reactivity represents the unhampered response of the vessels, we seem forced to the conclusion that it is due only to the removal of tonic impulses normally playing on the vessels. But it is difficult to see why the removal of constrictor impulses alone should render the vessels more responsive to

constrictor stimuli, and we would have to suppose the removal of dilator impulses as well. This, in fact, would be the obvious conclusion if the full regain of tone or increased responsiveness appeared immediately after nerve section. To account for its gradual development by the interruption of dilator fibres leads to other assumptions and difficulties which we may leave undiscussed. There is, however, another way in which we might imagine a gradual loss of dilator influences to occur. It might be that the continued hyperæmia, by washing away, reduces the concentration of the normal dilator substances in the tissues of the ear, Lewis (23) advanced this view to account for the pallor which tends to follow increased bloodflow to areas of the human skin. If this is so, then long continued hyperæmia caused, for example, by maintaining the body warm should also produce a regain of tone in the vessels supplying the part. When a normal ear is kept flushed in this way, there may be slight regain of tone but the regain is clearly surpassed by that developing in the denervated vessels (after about 24 hours), we cannot therefore in this way account for the increased responsiveness of the denervated vessels.

The views so far discussed assume that the muscle fibres of the vessels are themselves unaltered and that the state of tone of these fibres is the result of the various chemical influences, or in other words, on the relative amounts of constrictor and dilator substances acting on them. Another and different point of view remains to be considered. It may be that the sympathetic nerves contain fibres which exert a trophic influence on the smooth muscle of the vessels, and that the interruption of these fibres leads to an enhanced responsiveness perhaps, for example, by rendering the muscle fibres more permeable to chemical substances or perhaps by interfering with the mechanism rendering stimulating bodies inert, and so allowing them to produce a greater effect. From the point of view of trophic influences we may consider briefly other effects of denervation on the tissues of the ears.

Other effects of denervation It is now becoming more clearly recognised that many of the changes seen in denervated limbs, and in the past ascribed to the interruption of trophic nerve fibres, are in reality secondary effects of loss of sensation or movement. (Contemporary observations in this laboratory, *see also* (17).) From this point of view, the rabbit's ear is particularly well suited for observations, it can be deprived of its nerve supply without disturbing motor function and it is not liable to injury if the animals are kept in separate cages. We have kept many rabbits with one ear deprived of either all its nerves or of its sympathetic nerves only under observation for three months and a number for longer periods, up to a year and a half. In none of these animals have we detected any difference between the effects of sympathectomy and total denervation and we have not seen any "trophic" effects that cannot reasonably be attributed to alterations in the blood supply to the ear.

Thus, usually, the denervated ear becomes a little more scurfy and the hair grows faster on it than on the normal side, both of which effects are most likely due to the average higher temperature of the denervated ear (from increased bloodflow through it) stimulating the epithelial tissues to increased growth (Fig 12) It is presumed that, under the quiet and confined conditions of a cool animal house, the average temperature of the denervated ear is higher than that of the normal We have never seen "trophic" ulceration of the denervated ear and, in fact, injuries caused intentionally by cutting, burning and chemically, heal just as well and as quickly as, and sometimes more quickly than, similar injuries on the normal ear We have noticed also, that the hair immediately around these injuries grows more quickly than elsewhere on the denervated ear In young rabbits, denervation does not interfere with the growth of the ears, though we have not found, as have Harris and Wright (16), that it leads to increased growth in length (observations on nine rabbits) We have failed to detect any structural change in the blood vessels as a result of denervation, although we have looked for the medial and intimal changes described by other workers* (19, 21, 32) Lastly, we have found that even in the denervated adult ear, by ligating the main arteries, the blood vessels can be stimulated to new growth to form a collateral supply just as well and as quickly as in the normal ear Nothnagel (30) also found that denervation in no way hindered the development of collateral circulation in the rabbit's leg These observations, then, bring no evidence to support the idea of a direct trophic influence of the nerves on the vessels or other tissues of the ear

Before leaving unsolved this question of the enhanced responsiveness of the denervated vessels attention may be drawn to the corresponding case of the pupil of the eye In the rabbit and cat, after section of the cervical sympathetic cord, the dilator muscle of the pupil becomes abnormally sensitive to the action of adrenaline (28) and under conditions of excitement and asphyxia, etc, the paralysed dilator is stimulated to contract and becomes larger than the normal It has long been known (2) that this paradoxical dilatation is increased by removing the superior cervical ganglion So far, the changes in the eye are closely parallel with those in the ear but Kellaway (20) has shown that removal of the adrenals prevents the paradoxical dilatation after asphyxia in the cat, except as a residual effect after very severe asphyxia, we have seen that the constriction of the denervated vessels remains unchanged in the rabbit Other instances are known of a heightened responsiveness of smooth muscle to adrenaline after denervation and Cannon and Bacq (5) suggest that it may be due to an accumulation of sympathin within the idle cells

* We have also examined vessels of all sizes from the forelimbs of three cats in which one foreleg had been deprived of its sympathetic supply by Harris and Wright (16) 11, 12 and 23 months previously We could detect no difference between the vessels of the two sides

CONCLUDING REMARKS

Little is known about the vascular effects of denervation in man. It is known that after nerve section there is an initial loss and a gradual regain of tone, and recently Freeman, Smithwick and White (11) have shown that human vessels deprived of their sympathetic supply are abnormally sensitive to the action of adrenaline. It remains to be determined if the other phenomena witnessed in the rabbit are paralleled in the human subject. It has been shown previously that there are differences in the vascular mechanisms in the rabbit and man. Thus, the local axon reflex is much less distinct in the rabbit* (13), there are apparent differences in the mechanism of the reaction to cold (14). Again, in the rabbit, sensory denervation does not alter the effects of sympathetic denervation, yet in man it would seem that a limb deprived of its sympathetic supply only tends to remain warm but if a mixed nerve is cut, the limb tends to become cold (25). Whether this is an effect of sensory denervation or whether it is the result of paralysis of the voluntary muscles remains undetermined.

The enhanced responsiveness of the denervated vessels is not only of physiological interest but has a bearing on the diseases of the peripheral vessels in man. The recent work of Lewis (24) has shown that the Raynaud phenomenon is due to a local fault of the vessels, they are abnormally sensitive to the local action of cold. The nature of this fault is unknown, it appears to be associated, in its severer manifestations at least, with local structural changes of the vessel wall, but whether as a result or a cause is undetermined. If local disease precedes the Raynaud phenomenon the latter may be the result of local interference with the nerves of the vessel.

The observations on the rabbit also suggest that the occurrence of Raynaud attacks in man after sympathectomy may be due, at least in part, to a circulating adrenaline-like substance which, as we have seen in the rabbit, is released under conditions of nervous stimulation. Further, if the phenomena of the regain of tone are the same in man as in the rabbit, then it would seem that when operative measures are undertaken for the relief of peripheral vascular disease, preganglionic section is preferable to ganglionectomy, thus reducing the subsequent reactivity of the vessels.

* Although the local axon reflex elicited by local mechanical or chemical stimulation (including histamine) is very limited in its extent, a conspicuous and widespread flush can be produced by local faradisation. As in man (26), faradism is exceptional in that it is easy to produce a conspicuous flare with little or no whealing of the skin. We have evidence for the rabbit that the flushing produced by faradism through the local axon reflex is of the same nature as that produced by antidromic stimulation of the sensory nerve trunks, in both, vessels of all classes are widely dilated and the dilatation is long enduring. We believe that the released substance responsible for the dilatation is neither histamine nor acetyl choline, alone or in combination.

Lastly, it would seem reasonable to suggest that an increased concentration of the adrenaline-like substance may be responsible for the pallor of the skin in conditions of ill-health in man and that, by raising the level of rectal temperature at which normally innervated skin vessels relax, it may play a part in the production of fever. An observation by Johnson, Scupham and Gilbert (18) is significant from this point of view. By injecting foreign protein they produced fever in a patient from whom the right stellate and first and second thoracic sympathetic ganglia had been excised for arthritis. They noted that during the fever there was a marked increase in the peripheral pulse volume of the normal left fingers, while there was no significant change in that of the right side. Examination of the plethysmographic records in their Fig 3 shows that with the fever there is not only no increase but a decrease in the pulse of the denervated side, which passes off as the fever subsides. This decrease may be interpreted as evidence for an increased concentration of the adrenaline-like substance exerting a stronger constrictor effect on the denervated vessels, it may even be responsible for the fever itself. It may be noted, however, that Pinkston (29) does not find a constant vasoconstriction in the sympathectomised ear of rabbits during the fever produced by the injection of typhoid-paratyphoid vaccine. What part this unknown substance may play in maintaining normal vascular tone and body temperature must be left for future determination.

APPENDED NOTE BY R T GRANT AND R BRUCE PEARSON
(*From the Clinical Research Unit, Guy's Hospital*)

Observations on the effect of struggling have recently been made on a patient from whom the left lumbar sympathetic ganglia had been removed six months previously for the alleviation of pain in the left foot due to thrombo-anglitis obliterans. The left leg and foot were warm, sweating was absent from the leg except on the front of the thigh. When the patient was cool, the right foot was colder than the left but became warmer when the patient was warmed up, the left foot remaining unaltered in temperature. In three observations it was found that when the patient (warmed and sweating freely) struggled with his arms and body against resistance for one minute, the legs being still, the temperature of the left great toe quickly fell 2° and then slowly returned to its previous level. The struggle caused a temporary rise (20 mm Hg) in systolic blood pressure. The right great toe showed no fall of temperature. The subcutaneous injection of one minim of 1 in 1,000 adrenaline caused a similar fall and slow return of the left toe temperature without affecting that of the right. It would seem therefore that the denervated vessels in man react in the same way as in the rabbit.

SUMMARY

1 Observations are recorded on the normal control of vasomotor tone in the vessels of the rabbit's ear and the vascular and other effects of denervation are described

2 Evidence is given to show that the regain of vascular tone following denervation is due to an increased responsiveness of the denervated vessels to various stimuli, including an adrenaline-like substance circulating in the blood stream

3 The source of this adrenaline-like substance is unknown, it comes from neither the adrenals nor the pituitary body, it is unlikely to be sympathin. Its concentration in the blood is increased by nervous or muscular activity, it is reduced by rest

4 The nature of the increased responsiveness of the denervated vessels is discussed but left undetermined

5 It is suggested that the adrenaline-like substance may play a part in maintaining normal vascular tone and body temperature, that an increase in its concentration may be responsible for the pallor of ill-health and for the rise of body temperature in fever

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VASCULAR REACTION, RABBIT'S EAR



Fig 7 shows a rabbit under luminal arranged for observation on the water bath. The thermometer in the rectum is held in position by a rubber band attached to the end of the thermometer and fixed to the body hair by a back of the thigh. A cannula with rubber tubing and spring clip attached is inserted into the vein in the back of the thigh. Thermal junctions are attached to the ears. The blood pressure capsule on the left ear is held in position by a clamp for taking the photograph. In practice it is supported by hand.

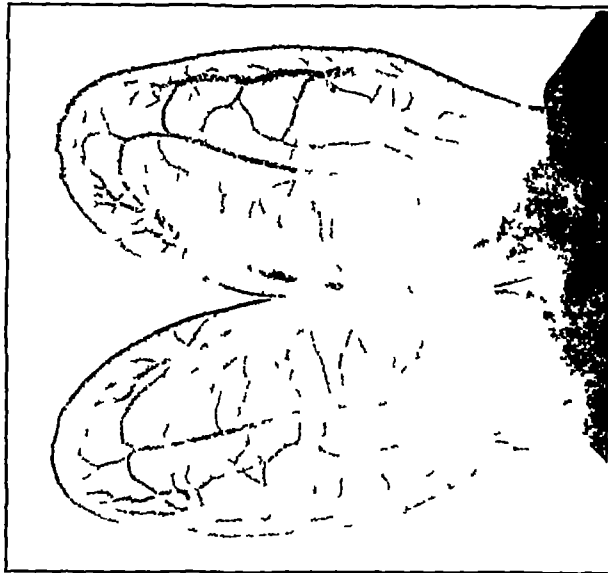


Fig 8

Fig 8 Rabbit under luminal The ears are viewed from behind by transmitted light Right ear normal fully flushed by raising body temperature, left ear freshly denervated The ears are equally flushed and their visible vessels equal in calibre

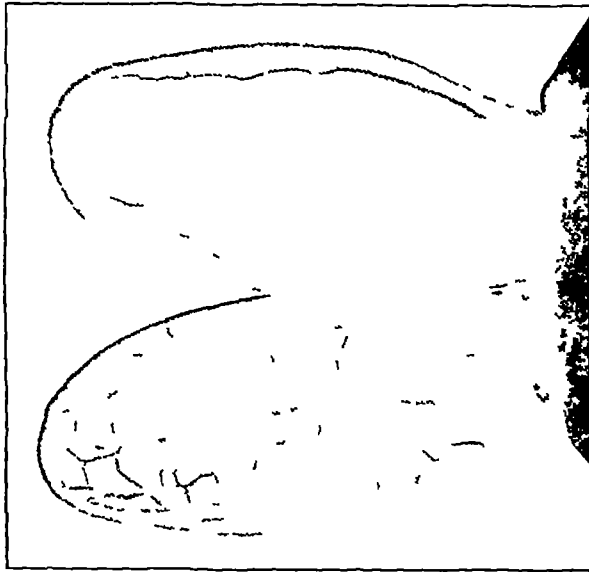


Fig 9

Fig 9 Same ears as in Fig 8, but the normal right ear vessels are now constricted by lowering the body temperature, the vessels of freshly denervated ear remain fully flushed

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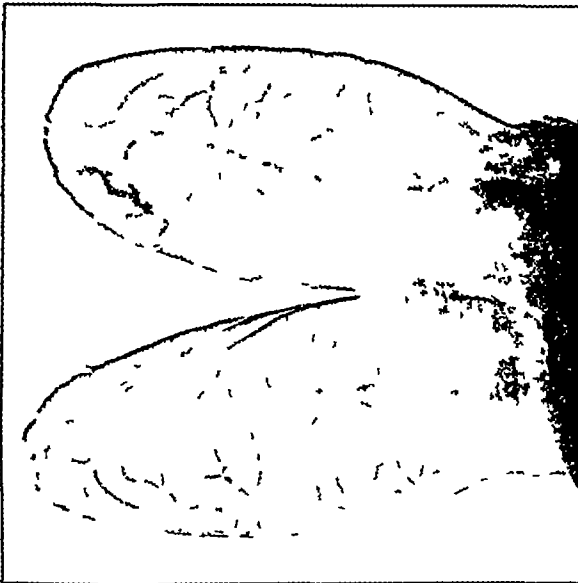


Fig 10

Fig 10 Rabbit under luminal 14 days after sympathetic denervation of left ear The right normal ear is fully flushed by raising body temperature The main vessels of the left ear are as dilated as those of the right but the ground colour is paler (actually paler than appears in the photograph) and fewer of its small vessels are visible

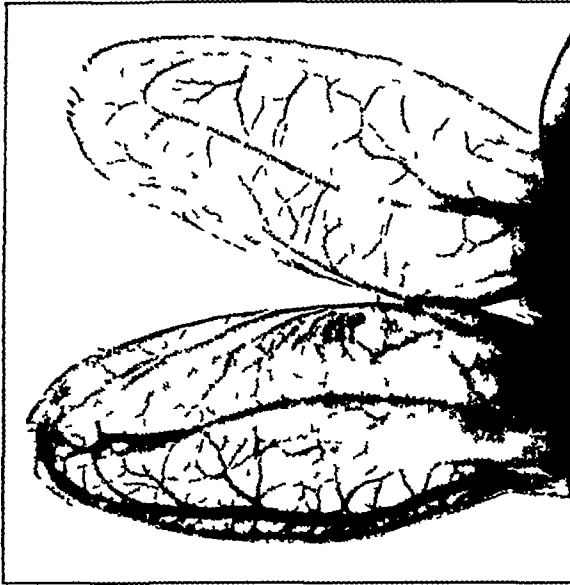


Fig 11

Fig 11 Same ears as in Fig 10, but after 5 min faradisation of peripheral end of the cut great auricular nerve The ground colour of the left ear is now considerably deeper (actually deeper than appears in the photograph) than that of the right and more small vessels are seen, the main vessels, being already fully dilated, remain unchanged



Fig 12 Photograph of ears, a month after epilation of both and sympathetic denervation on the left showing the greater regrowth of hair on the left denervated ear The difference is not always so conspicuous as in this example

THE RELIABILITY OF CLEARANCE TESTS FOR RENAL EFFICIENCY

By CUTHBERT LESLIE COPE *

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ELSEWHERE (3), we have called attention to the existence of evidence supporting the claim of reliability for the urea clearance test as a measure of the power of the kidney to excrete waste products. This evidence depends on the fact that other similar tests, using different substances, yield in the majority of cases, closely similar results to those given by the urea clearance.

In the present paper it is proposed to record comparisons of these several tests in support of this claim. The two other substances chosen for comparison with urea are creatinine and the sugar xylose †. Creatinine has been used because it has been widely employed in Scandinavia, and to some extent also in America, as an alternative test to the urea clearance test. Xylose has been used because it seemed at one time to offer hope of providing a method of distinguishing predominantly tubular from glomerular types of renal damage. That this hope has not been fulfilled in no way vitiates the conclusions which are to be drawn here.

Methods

It is now widely recognized that spontaneous variations of functional efficiency do actually occur as a normal phenomenon in a given kidney. Hence for more reliable comparison of the tests, and in order furthermore, to eliminate the errors produced by incomplete bladder emptying, it was desirable to make the comparisons simultaneously rather than at different times. The clearances for these three substances have therefore all been determined simultaneously in each individual.

For this purpose 15 g of urea, 3 g of creatinine and 30 to 50 g of xylose were given by mouth dissolved in 500 c c or more of water. After allowing one hour for absorption into the blood stream, urine was collected throughout the next hour, and at the middle of this period blood was taken from an antecubital vein. Analyses for all three substances were made in blood

* (Senior Beit Memorial Research Fellow)

† Our thanks are due to the United States Chamber of Commerce for kindly supplying the xylose used in these experiments.

plasma and in urine. From the results the clearances were calculated according to the usual formula $\text{clearance} = U V/B$. The clearance represents that volume of blood which would contain the amount of a given substance which is excreted in the urine in unit time. The unit chosen is usually a minute, and the clearance is calculated by multiplying V , the volume of urine excreted per minute, by the ratio of $\frac{U}{B}$ where U and B represent respectively the concentrations in urine and blood of the substance under consideration. Thus if the urine is being excreted at the rate of 3 c c per minute, and the concentrations in urine and blood are 480 and 40 mg respectively, then the clearance is $3 \times \frac{480}{40} = 36$ c c per minute.

Thus all the clearance values have been obtained after the administration of urea. In the great majority of cases a good diuresis was also established. In two the volume of urine was less than 120 c c per hour, and in these the urea clearances were corrected according to the formula of Van Slyke. No similar corrections were applied to the creatinine and xylose clearances since there is good reason to believe that these clearances, unlike that for urea, are but little influenced by reduction of the urine volume.

Urea was determined in both blood and urine by the urease and aeration method of Van Slyke and Cullen (15). Creatinine was determined in both fluids by Folin's colorimetric method using a 1 in 5 tungstic acid filtrate of plasma and a suitable dilution of the urine (9, 10). Plasma xylose was estimated as non-fermentable sugar in the 1 in 5 filtrate obtained after precipitation of the proteins and most of the non-glucose reducing substances by copper tungstate according to the method of Somogyi (13). As sugar reagent Somogyi's modification of the Shaffer-Hartmann solution was used (14). Urinary xylose was determined in a similar way. Interfering substances were precipitated with copper tungstate, and the filtrate after suitable dilution was fermented with washed yeast and estimated for reducing sugar with the same reagent as was used for the plasma xylose.

Results and discussion

For convenience and simplicity in presenting these comparisons, it has been found desirable to express the renal functional efficiency indicated by each substance as a percentage of the average normal efficiency, rather than as an actual clearance value.

In order to do this it was necessary to establish a "normal" clearance value for each substance with which to compare the deviations found in nephritic kidneys. For urea this normal clearance figure is already recognized to be 75 c c per minute. Since in our experience, a urea clearance of 75 c c per minute has been found equivalent to a creatinine clearance of 210 c c per minute and to a xylose clearance of 86 c c per minute, we have taken these figures as representing 100 per cent functional efficiency by the creatinine and xylose tests respectively. A percentage value for the actual

functional efficiency of any nephritic kidney can thus be found by comparing the clearance actually obtained with these "normals" considered as 100 per cent. And this percentage function can be arrived at by means of creatinine or xylose in precisely the same way as it is more usually obtained by urea in the orthodox maximum urea clearance test.

The value which we choose for the normal creatinine clearance is rather higher than the average normal found by Rehberg (12) or by Ellis and Soma Weiss (6) whose mean was only 147 c c per minute. This difference may be due either to the different conditions under which our determinations were carried out, or to differences in analytical technique.

Our xylose clearances also are rather lower relative to both urea and creatinine than those reported on normal human subjects by Jolliffe and Chasis (11). These workers found the average ratio between the three

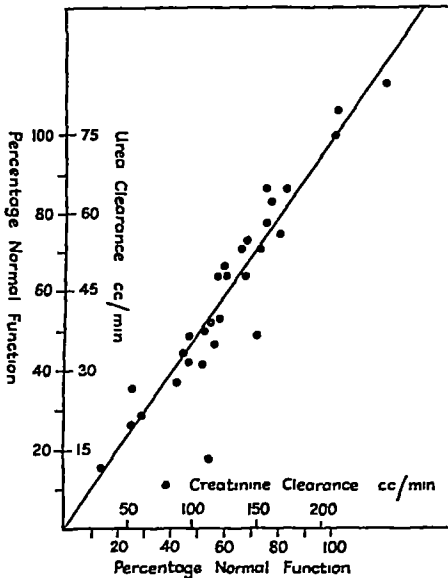


Fig 1

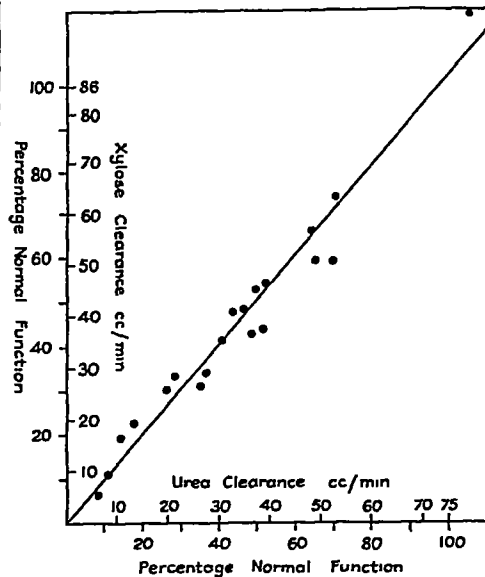


Fig 2

clearances of creatinine, xylose and urea respectively to be 100 57.9 40, whereas our own figures show a mean ratio of 100 41 36. Relative to creatinine our xylose clearances are however, in good agreement with those of Dominguez and Pomerene (5) who find the latter to average 42 per cent of the former compared with our own 41 per cent.

But it is the comparative results rather than the absolute values with which we are primarily concerned here and such discrepancies are not of great importance for present considerations.

A comparison between the simultaneously determined urea and creatinine clearances on a series of nephritic subjects of varying degrees of severity and of various types, is shown in Fig 1. In these 31 consecutive

cases only two deviate seriously from the general parallelism evident between the results of the two tests. For these discrepant figures we have no explanation to offer. It is of interest that they appear to be comparable to the cases reported by Ferro-Luzzi (7). Ferro-Luzzi interprets his own as cases of excessive urea reabsorption in the tubules, but such a conclusion is not as yet supported by sufficient evidence. But with the exception of these two cases, the "percentage normal function" as estimated by creatinine agrees well with that found by the use of urea. The widest discrepancy between the two tests shows 70 per cent renal efficiency by the creatinine method and 50 per cent by the urea clearance. The results of this series may thus be regarded as confirmatory of those earlier reported (2).

The agreement between the urea clearance and the xylose clearance test is shown in Fig 2, (see also Table). In this series of 20 consecutive cases no

Comparison of three methods of measuring renal efficiency

Disease		Percentage of full normal efficiency as estimated by—		
		creatinine	urea	xylose
1	Glomerulonephritis with marked "nephrotische Einschlag"	70 97	— —	80 108
2	Glomerulonephritis with marked "nephrotische Einschlag"	137	152	—
3	Uræmia of gastric alkalosis	266 280	267 208	313 336
4	Chronic glomerulonephritis	268	355	295
5	Acute nephritis	383	137	190*
6	Acute nephritis (later)	535	179	220*
6	Chronic glomerulonephritis	435 595	445 530	465 525
7	Cardiac failure Mitral	455 462	422 490	— —
8	Toxæmia of pregnancy	488	415	400
9	Acute nephritis	515	480	485
10	Chronic glomerulonephritis	525 595	505 648	512 595
11	Chronic glomerulonephritis	540 755	520 650	437 650
12	Acute nephritis	580	640	—
13	Acute nephritis	610 740	— —	688 735
14	Acute nephritis	660	715	745
15	Hypertension	670	735	—
16	Chronic glomerulonephritis and cardiac failure	715	485	428*
17	Auricular fibrillation	750	780	—
18	Normal	755	870	—
19	Acute nephritis (recovery)	760	820	—
20	Acute glomerulonephritis	790	600	—
21	Acute nephritis (focal)	730	700	590
22	Acute nephritis (recovery)	825	860	—
23	Normal	1000	1001	—
24	Acute nephritis (focal)	1070	880	—
25	Acute nephritis (focal)	1010	1070	1190
26	Normal	1190	1160	—

NOTE—Seriously discrepant results are marked with an asterisk.

seriously discrepant values have been encountered, and the agreement is even better than that between creatinine and urea

This agreement of both the xylose and the creatinine tests with the urea clearance thus affords evidence that all three are reliable in providing an estimate of the excretory efficiency of the kidney towards waste products, and it is the presentation of this evidence which is the main purpose of the present paper

It is not intended to suggest that either the creatinine or the xylose test should replace the urea test for clinical purposes. They have only been used here to obtain evidence of the reliability of the latter

But apart from this purely practical implication of the results, certain points of more theoretical interest also arise. Thus those who seek to apply the filtration-reabsorption theory to the nephritic human kidney may be tempted to draw conclusions from these results in support of that theory. For, if Rehberg's contention that creatinine excretion gives a measure of the glomerular filtration rate be accepted, then it can be deduced from our results that the concentration of reabsorbed urea bears an approximately linear relation to the concentration of urea in the glomerular filtrate. Although such a deduction is an attractive one for adherents to this theory, it must be received with caution. For it is simple to show mathematically that any substance whose clearance bears an approximately constant relation to the creatinine clearance, whatever the reason, must show the same apparent properties. We feel therefore that such deductions cannot be brought forward in support of Rehberg's hypothesis, and further, that the results are explicable equally well on either theory of renal function

It was our hope originally to be able to detect by means of these comparisons functional differences between tubular and glomerular types of renal damage. Both the rival classical theories of renal function agree in supposing that differences in the excretion rates of various substances are referable to the activity of the tubule cells. It might be expected therefore that tubular damage predominating over glomerular would lead to a tendency of the urine to approach the glomerular type. All the available direct evidence tends to show that the glomerular filtrate has the same percentage composition as blood plasma, and that those urine constituents which pass through it from the blood are all treated equally. From this it must follow that in a purely glomerular urine the clearances for all these substances will be equal. But our results have shown that in the final urine the three substances studied are excreted with widely different clearances, the ratio between them being approximately creatinine 100, xylose 41, and urea 36. An approach to a more glomerular type of urine should thus be shown in a tendency for the creatinine clearance to approach in value the clearances for xylose and urea. And this should be true whichever theory of renal function is in fact the correct one. But no definite evidence of any such tendency has been found. The material studied has included a variety of types of renal impairment, but the ratio between the three clearances remains

essentially the same in advanced nephritis as in the normal. Nor is it altered in cases with a predominantly nephrotic element in which tubular damage might have been expected to predominate over diminution of glomerular filtering power.

Thus our findings are not readily compatible with the frequently held view that the urine in advanced nephritis tends to resemble in constitution the glomerular filtrate.

They do however, tend to give quantitative support to the so-called Unitary View of nephritis, as upheld by Fishberg (8). This maintains that renal damage tends to impair the various partial functions of the kidney in equal degree and does not discriminate between them. It is because of this that we have been able to obtain agreement between estimates of renal efficiency made by studying the excretion of three entirely different substances.

But these substances have certain points in common. In the first place they are all substances in which so far as is known, the body has no further interest, and as such would appear to be representative of a large group of waste products. In the second place they all appear to be non-threshold substances. That is, they are all excreted by the kidney whenever they exist in the blood. There is no blood concentration for any of them below which the kidney ceases to continue their excretion. Thirdly, there is an important point of similarity in the phenomena presented by their excretion. This is a linear relation between the rate of excretion of each and its concentration in the plasma, and this relation is independent of the actual volume of urine excreted. Such a linear relation has been shown for creatinine by Cope (2) and by Dominguez and Pomerene (4). It has been demonstrated for xylose by Dominguez and Pomerene (5), and has been shown for urea by Addis and Drury (1) although in the latter case the relation only holds when the volume of urine is fairly large. Thus the excretory phenomena presented by these three substances, although still complex, are nevertheless among the simplest to be found for any urinary constituent. It is solely owing to these facts that it is possible to predict with some approach to accuracy the expected excretion rate for each substance when once the blood concentration is known. Then by comparing the expected excretion rate with that actually found, a measure of the renal efficiency is obtained. This is the principle which, in fact, has been employed here of calculating the clearances. For the clearance may be regarded as a mathematical short cut or aid in comparing the expected with the actual excretion rates. It is the outcome of empirical observation rather than of theoretical deduction and for clinical purposes at least, nothing is lost by regarding it simply as a mathematical formula for converting observed analytical figures into an estimate of renal efficiency. The extent of its success in doing this we have attempted to show in these comparisons. They are, so far as we are aware, in better agreement than reported comparisons between any other pairs of renal function tests. We therefore feel justified in claiming for the

urea clearance test a greater reliability in measuring the extent of impairment of the kidney power to excrete waste products than can at present be claimed for any other type of test

SUMMARY

Estimates of renal function in nephritic subjects have been made by the urea clearance test and by two independent methods, namely the clearance of creatinine and of xylose. In the majority of cases the results of all three tests are in good agreement. It is claimed that this fact provides considerable support for the claims of reliability as a measure of renal function made for the urea clearance test. Certain theoretical implications of the results are briefly considered.

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THE MANNER IN WHICH NECROSIS ARISES IN THE FOWL'S
COMB UNDER ERGOT POISONING*

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RECENT studies of spasmodic arrest of the circulation to the fingers, Raynaud's phenomenon, have led us to suspect that these attacks when frequent and severe may possibly result in disease of the vessels (4 and 5) The suspicion arises out of the association of Raynaud's phenomenon and digital arterial disease, and out of Thoma's many observations (8) showing that when bloodflow through an artery is stopped permanently by ligation, intimal thickening and shrinkage occur in the vessel The manner in which the changes described by Thoma come is unknown and it is unknown if similar changes would follow intermittent closure of arteries, or their almost complete closure over such periods as are experienced by patients exhibiting Raynaud's phenomenon

It was thought that relevant facts might have been gathered in previous work on ergot poisoning, but a search of past records has failed to yield quite the desired information It was stated long ago by Kobert (3) and Recklinghausen (6) and the statement has been confirmed by Grunfeld (2), Grigorjeff (1) and others (7), that when gangrene appears in the cock's comb after such poisoning, thrombi are to be found in the vessels, but the descriptions do not decide with sufficient clearness the relation of this thrombus formation to tissue necrosis The thrombus might be responsible for the final obstruction and lead to gangrene, or tissue necrosis consequent upon simple arterial spasm might be responsible for thrombus formation in the necrosed and immediately adjacent area From this standpoint an examination of the state of the vessels within the area of necrosis may obviously be of lesser importance than their state at some distance away, or their state before necrosis supervenes From these points of view new observations have seemed desirable

* Work undertaken on behalf of the Medical Research Council

Observations upon the living

Preliminary trials led us to use white Leghorn hens, because the comb in the hen, being far less bulky than in the cock, is more readily examined in serial sections. The hens were yearlings and selected as having perfectly formed, undamaged combs. Gangrene of the comb is usually produced in these birds by 3 or 4 daily doses of 10 mg ergotoxine base, dissolved in the form of ethane sulphonate* in 2 c.c. of acetone and injected into the breast muscles. Pallor of the comb and wattles, and especially of the skin around the eye, is obvious within 2 to 4 min of injection, it rapidly gives place to cyanosis (beginning at the 6th to 8th min), which develops especially in the digitations of the comb. The fall in temperature begins in the first minute and is completed in about 15 or 20 min, when the reaction is at its height (Fig 1). The

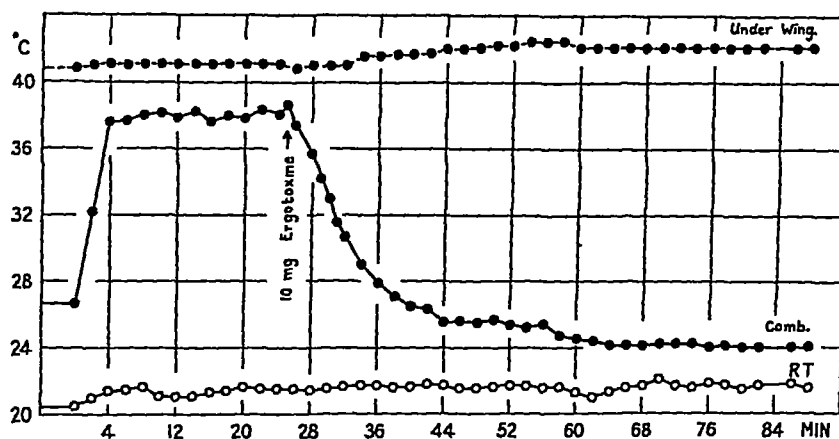


Fig 1 Hen 2 Under wing temperature, temperature of the base of a chief digitation of the comb, and room temperature (R T) The chart shows the quick rise of temperature in the originally cool comb, after placing the hen on the warm table. Later it displays the reactions of the warm comb to an intramuscular injection of 10 mg ergotoxine. It is to be stated that under wing temperature, owing to the thinness of the wing, cannot be regarded as accurately representing body temperature. It is to be noted that the temperature of the comb does not fall quite to room temperature under ergotoxine.

respirations are raised from the normal level of 30 or 35 eventually to 180 or 200 per min, the wings droop and there is some instability of posture. In some hours respiration begins to slow again, food is soon taken and the hen seems at ease, but the cyanosis lasts and is still conspicuous next day.

The hen has been made to sit daily on a flat metal box through which water flows at about 45°C, the body of the hen being covered and held down by broad cloths, temperatures are read from thermal

* Supplied by British Drug Houses

junctions attached to parts of the comb and beneath one wing. In control observations before injections, the temperature under the wing is ordinarily 40.3° to 41.8° , and this temperature rises by 1° or 1.5° in a half-hour's warming on the box. The original temperature of the comb, the hen coming from a cool room, has usually been low, the comb is then usually a little cyanotic and the middle and base of chief digitations register 23° to 25° (room temp 18° to 20°). It is the rule for these comb temperatures to rise (Fig. 1) to 34° or 36° within a few minutes (always within 10 min) of the hen being placed on the warm table, and for the comb to assume a deep and bright red colour.

On the day following the first injection of ergot this vasodilatation to body warming fails, the temperature of the comb remains substantially unchanged, or rarely rises a few degrees, even if body warming is continued for an hour and the table temperature is raised to 47° . The vessels of the comb will not dilate under conditions ordinarily producing full vasodilatation, neither will they relax if in addition the comb is directly heated to 41° or 42° , the circulation to the comb remains extremely sluggish, its colour is deep and fully cyanotic, and when blanched by pressure the colour flows back slowly into it. The circulation to the comb is not lost, however, for, as stated, blood will flow in it, and its temperature remains 2 or more degrees above room temperature. In the days after ergot has been given the under-wing temperature is 1° or 2° below normal and on the warm table rises less than in control observations.

If only one dose of ergotoxine is given, recovery of vasodilatation to body warming is usually demonstrable on the second day after injection (in 48 hr) but it is incomplete until the third, and occasionally until the fourth, day. To maintain a state of extremely slow circulation through the comb, the dose is repeated day by day. If dosage is stopped after several injections have been given, the circulation becomes restored within 48 or 72 hr to the parts of the comb that have not passed beyond the stage of simple cyanosis to the states of threatened or of actual necrosis, to which they are usually brought by four successive daily injections.*

Simple cyanosis of the digitations continues from the first injection onwards till the day following the 3rd or 4th injection, the colour of parts of the digitations then deepens, though the tint does not become more cyanotic. The digitation has an appearance as though blood were extravasated superficially into its tissue, and the skin can no longer be blanched by pressure. Digitations in this state cannot be cleared of blood by perfusing them after death, even if massage is used, sections subsequently show the capillaries to be full and the contents of the kind subsequently to be described. Usually this deep purple skin is marked off sharply from the adjoining cyanotic skin, in other instances outlying islets of the deep purple colour occur at the margin, or the transition

* Frequently the skin over the crop becomes extensively necrosed about the same time

is gradual. It is usual for the digitation to become affected in this way for half or the whole of its length, there may be an extension into the main part of the comb as well. If injections are stopped at this stage, some recovery of the comb may occur by the next day and considerable recovery is usual by the day after. After this interval the base of the comb has become warm and fresh in colour, the grip of ergot having relaxed, and this fresh colour has gradually invaded the bases of the digitations, displacing all cyanosis and pushing back the deep purple areas of discoloration. Simultaneously, however, the very tips of one or more digitations are noticed to be drying, becoming obviously shrunken and brown, these tips are the only parts that fail to recover.

Thus, there are three chief stages, namely, (a) a stage of cyanosis from which recovery is rapid, (b) a stage of deep purple colouration, in which blanching cannot be effected by pressure, and from which there may be slow recovery or no recovery, this is the stage of lost circulation, or as we shall call it for brevity, the stage of stasis, (c) a stage of necrosis.

Histology

The comb may be described briefly. It has an outer covering of well developed epidermis (Fig 4). Beneath this is a thick layer of cavernous tissue, characterised by closely set capillary tubes, very distinctly lined by epithelium and lying in a reticulum of fibro-elastic tissue, this fibro-elastic tissue becomes denser in its central parts where it supports the small arteries and veins and contains relatively few capillaries. In the centre of the comb are its main vessels, lying embedded in a framework of connective tissue which usually contains large masses of fat cells also.

Cyanosed comb Sections cut through formalin fixed digitations, taken during the stage of simple cyanosis, and compared with similar sections of normal combs, show no more than a little engorgement of the capillary vessels of the cavernous tissue.

Stasis Sections through parts of the digitations, presenting the signs of stasis during life, show intense engorgement of the capillaries of the cavernous tissue, in this engorgement the main vessels often participate. The capillaries are widely dilated and press against each other closely. When the stasis has persisted for two or more days the blood within most of the capillaries is notably changed. In most of the capillaries a chief content of the vessel is a mass of homogenous substance the staining of which is almost uniform, it stains chiefly with acid dyes, but when hæmatoxylin and van Gieson's stain have been used it colours more deeply, taking up a reddish or brown tint. The substance is apparently separated plasma, for a similar appearance is seen in normal combs that have been clamped off, cut away and merely allowed to stand for 6 to 30 hours before fixing. The hyaline masses have been described previously by Grigorjeff (1) in his studies of ergot poisoning.

When this hyaline first appears in the capillaries the red blood cells of the capillary are usually embedded in it, and their envelopes are still distinguishable. Later, in the ergot poisoned comb, the cytoplasm of the red blood cells becomes indistinguishable and the nuclei have the appearance of being closely packed together in masses (Fig 5). In some capillaries hyaline only is found, in some only massed nuclei, but in most of them a mass of nuclei is enclosed with hyaline. Capillaries holding such massed nuclei or hyaline contents occur for the most part, but not exclusively, in the most superficial layers of the comb, the epithelium of the skin overlying them is in greater or lesser degree shrunk, and its staining reactions altered, the endothelial lining of these capillaries is indistinct or invisible. In the same digitations it is not unusual to find small areas in which red blood cells have extravasated in large numbers into the connective tissue and, when this has happened, a local leucocytic infiltration may also be present.

Necrosis Sections through tips of obviously drying and browning digitations, present manifest evidences of necrosis, the epidermal layer is shrunk, the capillaries and all central vessels are seen to be dilated and packed with the nuclei of red blood cells, but clearness of detail is everywhere lost.

Edge of necrotic area At the border of the necrotic areas and for a variable distance proximally it is the rule to find clots in the dilated central vessels. There are large and usually rounded masses of densely packed nuclei of red blood cells, the cytoplasm of the cells being indistinguishable, these masses occupy a large part of the lumen. Partly encircling them, or moulded to their sides, masses of fibrin are seen, the fibrin has not a purely hyaline appearance, it can be seen to consist of coarse and irregular strands or masses, between which some well-formed red blood cells, or many disintegrating red cells, and white cells are found, thus blood cells are set throughout most of these fibrinous masses, though more sparsely than in the case of the masses of packed nuclei previously described, into or through which also finer strands of fibrin may be traced. As the sections are examined further away from the necrotic area, these thrombotic masses gradually give place to accumulations of undamaged red blood cells. Hyaline masses occupying the whole lumen of the vessel, or almost surrounding a central collection of red blood cells, are seen occasionally in these sections. We think they have been mistaken by several previous writers for ante-mortem blood clot. But they are found equally in sections of normal combs and especially in those allowed to stand before fixing, separation of plasma and red blood cells seems to happen readily in all the small vessels of the comb. The characteristic feature of the ante-mortem clot in main vessels is the coarse strand of fibrin, this is associated with nuclear accumulations, which vary notably in density. In the sections, most thrombosed arteries are first recognised by their darkly stained contents,

the result of the crowded nuclei of red blood cells, which seem to have lost most of their cytoplasm (Figs 6 and 7) The appearance of these massed nuclei is exactly similar to that seen in the capillaries, as previously described We are not clear whether this massing of nuclei marks thrombi of a particular age, or whether it is chiefly an effect of dessication

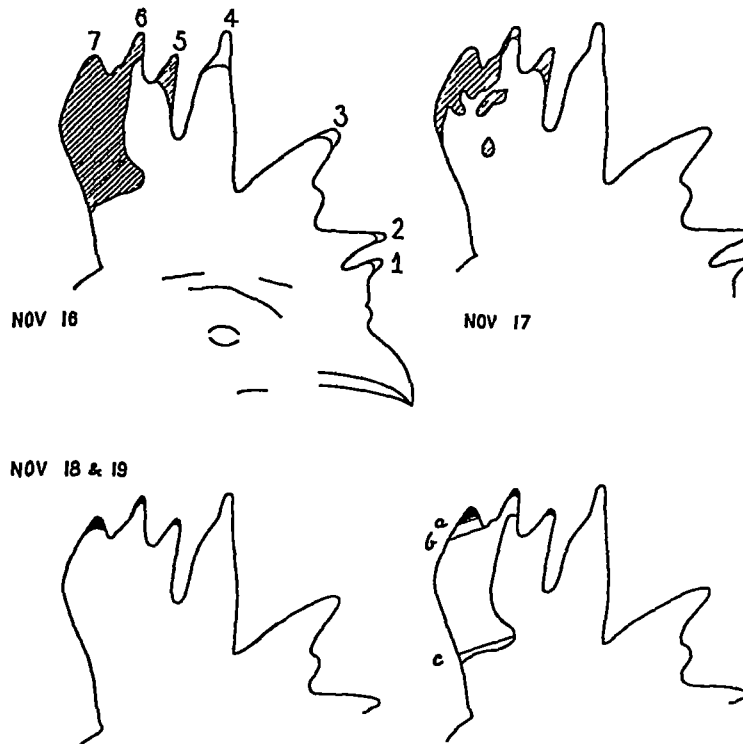


Fig 2 Hen 6 The extent of full cyanosis of digitations 1, 2, 3 and 4 is indicated by a simple line, areas of stasis by shading (5, 6 and 7), and areas of necrosis in black

In the junction of necrotic with normal tissue, it is the rule to find the capillaries of the cavernous tissue in a state of stasis with very many or most of them containing massed nuclei or hyaline masses, at the margin too it is not unusual to see the whole of the cavernous and central tissues infiltrated with leucocytes

The following examples will suffice to illustrate the main observations

Hen 6 received 3 injections of 10 mg ergotoxine on the 13th, 14th, and 15th of November, and no more On the 16th digitations 1 to 4 were in their usual cyanotic condition, but digitations 5, 6 and 7 and a considerable part of the adjoining comb had assumed the deep purple tint of stasis (Fig 2, shaded area) On the 17th this area of stasis had in part recovered, leaving two outlying islands, a little further recovery occurred when the hen was warmed on the hot table On the

18th the whole comb was red and warm except for the three small areas of dry gangrene at the tips of digitations 5, 6 and 7. The fowl was killed on the 19th and the comb fixed. Sections down to line *a*, showed necrosis, the lowest sections showing thrombosis of all vessels, capillaries, arteries and veins, and intense leucocytic infiltration of the tissues. From *a* down to *b* the thrombus extended in many of the arteries and some veins, all of which were dilated, the capillaries were engorged and some presented massed nuclei or hyaline masses. The superficial tissues also contained areas of hæmorrhagic extravasation. From *b* down to *c*, an area originally involved in stasis and still a little swollen when the animal was killed, the chief abnormality found was a quantity of hyaline substance, presumably inflammatory exudate, in the tissue spaces and lymphatics of the centre of the comb, throughout these sections, too, were groups of capillaries and isolated capillaries showing the familiar pictures of massed nuclei or hyaline. No thrombus could be found in the main vessels of this or any more proximal part of the comb. Sections of digitation 4 showed no more than slight congestion of the capillaries. This experiment illustrates the onset of stasis and its progress to necrosis. The necrosis was accompanied by vascular thrombosis, the clots extending a few millimetres proximal to the actual area of necrosis. Stasis in the largest part of the area to show it, was unassociated with clotting, and this area had recovered with rapidity.

Hen 9, received four injections of 10 mg ergotoxine on Nov 26, 27, 28, and 29, and no more. On the 30th, cyanosis and coldness were maintained over digitations 1 to 5, but the discoloration of digitations 6 and 7 was deeper and more sharply defined (Fig 3). On this day, too, a discoloration like a purpuric eruption appeared on the outer surface of the right-hand wattle. When this fowl was thoroughly warmed on Dec 1st the base of the comb became pink and warm, showing the ergotoxine spasm to have passed, but the digitations remained unchanged in colour and temperature. On Dec 2nd the cyanosis of digitation 1 had disappeared and the purple discoloration of all the remaining digitations had become well defined. By the 3rd there was noticeable drying of the tips of digitations 4 and 5. By the 4th the purple discoloration had receded a little in one or two places, and necrosis was obvious at the tips of all digitations 2 to 7. On warming the fowl, all but the discoloured parts of the comb became red and hot. The condition was unchanged next day, when the hen was killed.

Digitations 6 and 7 were examined in their length. From the necrosed region downwards to line *a* arteries and veins were found to be widely dilated and full of thrombus, much blood was extravasated diffusely into these sections, the capillaries were dilated and contained massed nuclei and hyaline substance. As the original line of discoloration (line *b*) was approached the thrombus in the main vessels became less frequent, and gross capillary changes less numerous, in the lowest sections from

this region the contents of only a few capillaries were altered. Below line *b* all the main vessels were normal, a few capillaries were packed with nuclei. All the more proximal sections down to line *c* were normal.

Sections of the 2nd digitation, showed necrosis at the tip and thrombosis of main vessels in its immediate neighbourhood, but lower down the main vessels of this digitation were normal. On the other hand capillaries were grossly affected in the whole length of the digitation down to line *d*, becoming less affected as the digitation was examined from tip to base.

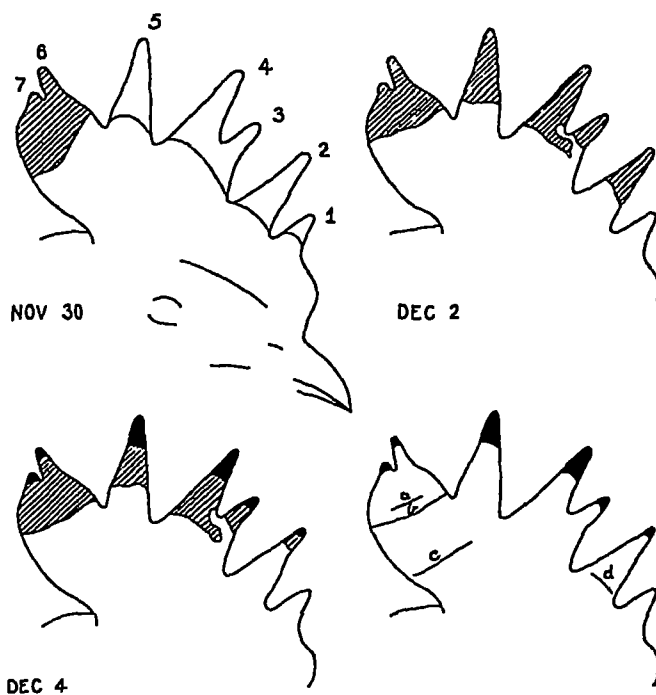


Fig 3 Hen 9 The method of indicating full cyanosis, stasis, and necrosis is the same as in the last diagram

Sections of the right wattle showed very little blood extravasation. The purpuric looking patches were groups of capillaries presenting the characteristic pictures of advanced stasis with altered contents previously described. The affected groups of capillaries were found only on the outer surface of the wattle, and the surface epithelium over each group was shrunk from drying. There were no thrombi in the main vessels.

When the relation of thrombus formation in the main vessels to necrosis of the end of the digitation is studied, in the manner indicated in these illustrations, it can be concluded that necrosis of the digitation occurs rarely, if ever, in the absence of thrombi. These are found not only within the necrosed area, but always extend for a little distance

proximally. In some instances, with necrosis only at the tip of the digitation, thrombi are found in central vessels as far as the base of the digitation. Not only main arteries but main veins are often thrombosed. When the condition stasis has been identified in the digitations during life, but has not proceeded to actual necrosis, thrombi are occasionally found in some of the central vessels. These facts demonstrate that thrombosis is not the sequel to necrosis, and point to necrosis being the outcome of thrombosis. But it is also clear that nutrition can suffer severely in the absence of thrombosis of the main vessels, and may lead up to simple stasis in the capillary vessels and to gross changes in their contents. If these capillary changes are closely aggregated they lead to so gross a defect in local blood supply that the epithelium overlying such areas of cavernous tissue becomes dry. Very possibly this process may by itself proceed to dry gangrene, though we have not seen this happen, by the time necrosis declares itself thrombi have appeared in main vessels.

Interpretation

The manner in which the tissues of the comb become damaged seems to be as follows—the poison ergotoxine constricts the arteries of the comb, this constriction is one that cannot be released by relaxation of vasomotor tone or by local warming. The constriction is maintained if ergot injections are repeated day by day, but it is insufficient to stop the bloodflow through the comb, which continues a little warmer than the surrounding atmosphere and shows at first no signs of dessication. But about the third or fourth day the nutrition of the walls of the vessel begins to suffer, for about this time stasis occurs in them, the blood in the capillaries being in a state rendering its dislodgment difficult. Histologically all the vessels and especially the capillaries are found to be dilated, the contents of the latter present the picture of massed nuclei or hyaline masses. When the circulation in the capillaries ceases, the overlying epithelium and later the contents of the engorged vessels begin to dry. It is impossible to declare precisely how far this process can be carried and the affected portion of the comb yet recover, though it is clear that recovery happens from the early but not from the later stages, as judged by the sequence of events witnessed during life. The nutrition of the walls of the main vessels suffers in the same way as does that of the walls of the capillaries, and clots form in arteries and veins, though in general a little later than the occurrence of stasis in the capillaries. Dilatation is the rule in any vessel in which blood flow ceases, whether it becomes thrombosed or not. We have seen no vessels in a constricted thrombosed condition, or indicating post-mortem relaxation of the walls away from a small central ante-mortem thrombus.

Briefly, the evidence favours the view that constriction of the arteries, continuing through several days of ergot poisoning, does not

lead directly to tissue necrosis, but to damage to the walls of the vessels, resulting in dilatation, and in stasis or in thrombosis, either of which will bring the circulation locally to an end and together determine dry necrosis of the corresponding tissues

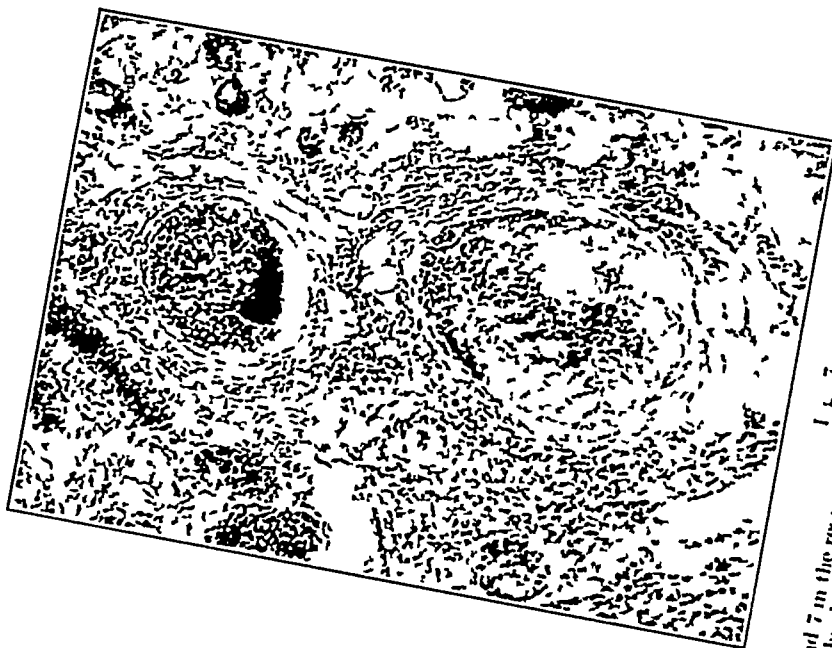
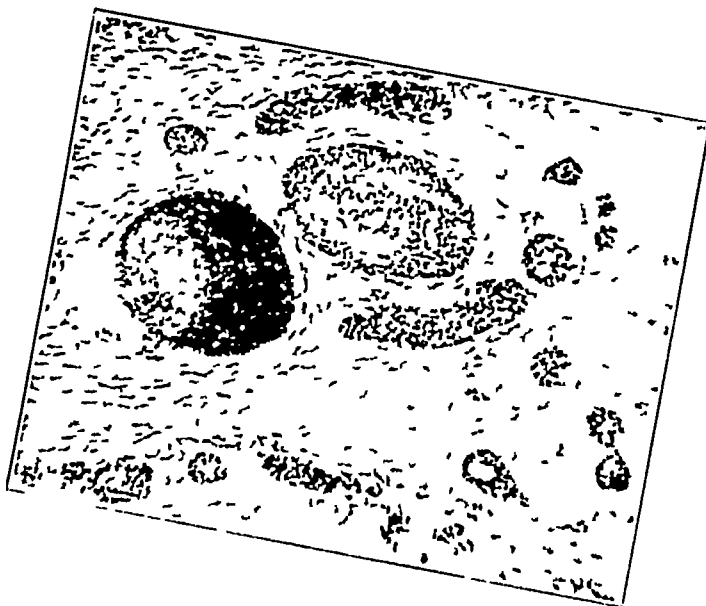
Ergot produces its ultimate effects entirely through arterial spasm continuing for 3 or 4 days, a direct poisoning of the tissues seems to play no part. All the effects witnessed in the comb can be reproduced by mechanical interference with the circulation. In a number of hens we have clamped the bases of digitations, including in the clamp three fourths or four fifths of the base of the digitation. Enough must be clamped to produce deep cyanosis of the end of the digitation within a few minutes, though the unclamped portion and some of the digitation distal to the clamp should remain red. Characteristic conditions of stasis and of gangrene of the tip of the digitation can be produced by maintaining the clamp for 48 hr, sometimes in as short a period as 30 hr. The histological appearance of simple stasis, of stasis complicated by dessication, the formation of hyaline masses or of massed nuclei, and of necrosis accompanied by *ante-mortem* thrombi in the main vessels, are all faithfully reproduced. It is usual in these experiments to find coagulated lymph in the central spaces of the digitation, a phenomenon which differs from that in ergot poisoned combs only in its greater frequency in the clamp experiment.

SUMMARY

Gangrene of the hen's comb can be produced regularly by day to day injections of 10 mg ergotoxine into the breast muscles. A constriction of the arteries, which is unrelieved by relaxing vasoconstrictor tone or by local warming, is thereby maintained and, though a little flow of blood continues, serious nutritional changes occur by the end of a few days. The endothelium of the vessels suffers, plasma is lost and stasis occurs in the capillaries, vascular clotting follows in central vessels, which are by this time dilated, and necrosis is determined. All these changes can be produced within a few days by mechanically impeding the bloodflow to the comb. Vascular spasm in ergot poisoning does not arrest the circulation, and so does not cause gangrene directly. The spasm profoundly slows the blood stream and leads to the secondary changes in the vessels described, these are responsible for the arrest of bloodflow, which in turn results in death of the tissues.

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FIGS. 6 and 7. H. n. 9. Parts of a transparent section below digitations 6 and 7 in the region marked by line *a* in Fig. 3. The so micro upper (x 120) are from adjacent parts of the central tissue of the digitation. Fig. 6 shows two chief vessels of which the nuclei are closely packed; thus upper vessel contains a pale staining, eosinophilic mass, the lower vessel contains irregularly arranged strands of fibrin and the nuclei of red blood cells. A dilated artery is seen above, containing small masses of fibrin, scattered nuclei and one small mass of thrombosed nuclei of red blood cells. Below this is a larger vessel almost filled with masses of fibrin, the lumen is filled by red blood cell nuclei set in all the vessel is shown the red blood cells are represented by nuclei only, their protoplasm being indistinguishable.

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OBSERVATIONS ON THE CAPILLARY PERMEABILITY IN CASES OF NEPHRITIS AND OF HEPATIC CIRRHOSIS WITH HYPOPROTEINÆMIA

By F H SMIRK

(From the Medical Unit, University College Hospital)

It is now beyond question that in nephritis there is a type of œdema in which the percentage of protein in the plasma and the colloid osmotic pressure of the plasma* are subnormal. This type of œdema occurs in nephrosis and in the nephrotic stage of glomerulo-nephritis.

It is generally believed that such œdema is caused partly by the low plasma C O P. The aim of the present investigation is to distinguish between the effects of a low plasma C O P and an increased capillary permeability in causing this œdema.

Baldes and I (1) using Hill's vapour pressure method have shown that the total osmotic pressure (total osmotic pressure = crystalloidal osmotic pressure + colloidal osmotic pressure, the crystalloidal osmotic pressure being much the greater) of œdema fluid and of plasma are equal (to within 1% or less) if time is allowed for the process of diffusion to smooth out irregularities caused by a temporary excess of metabolites in either the blood or the œdema fluid. This equality of the total osmotic pressures of œdema fluid and plasma is maintained despite considerable variations in the total osmotic pressure of the plasma.

This indicates that either water or water and crystalloids pass freely through the capillary wall so equalising the total osmotic pressures, and that the formation of œdema fluid is governed partly or entirely by simple physico-chemical forces.

Moreover, a chemical study (unpublished) and a survey of the literature both concerning the relationship between the composition of blood plasma and various types of transudate was made (5). Oedema, peritoneal, pleural, pericardial, joint and hydrocele fluids, aqueous humour of the eye, lymph, cerebro spinal fluid and dialysates and ultra-filtrates of plasma obtained in vivo and in vitro were considered. The results of 60 observers involving over 500 comparisons of the composition of plasma and transudate indicate that the relationship between the percentages of chlorine, sodium, bicarbonate

* Colloid osmotic pressure of plasma = Plasma C O P

calcium and urea in plasma and in transudates such as oedema fluid may be explained on a physico-chemical basis by Donnan's theory of membrane equilibrium

In other words the composition of a given transudate is substantially the same as the composition of the fluid obtained *in vitro* by ultra-filtration of the corresponding plasma through a dead membrane which is permeable to water and to crystalloids but is impermeable or relatively impermeable to protein. Simple filtration through blood vessels provides a satisfactory explanation of nearly all published data concerning the relationship between the composition of blood plasma and transudates. The varying protein content of these transudates is probably due to the fact that blood vessels in some situations are not completely impermeable to protein.

If oedema fluid is a simple filtrate of plasma the passage of fluid out from and back into blood vessels must depend upon the relationship between the capillary pressure, which furthers transudation, and the plasma C O P which furthers reabsorption of the fluid (6). In certain circumstances the mechanical resistance of the tissues to distension and the colloid osmotic pressure of the oedema fluid will play a part. The colloid osmotic pressure of the oedema fluid in nephrosis and in the nephrotic stage of glomerulo-nephritis is so small that it can be neglected. A fall in the plasma C O P must, therefore, increase the rate of formation of oedema. Also, if oedema fluid is a simple filtrate of plasma, another governing factor of the rate of formation of oedema fluid must be the capillary permeability. An increase in the permeability of the capillary blood vessels of a limb may mean either loss of some of their normal resistance to the passage outward of the plasma protein, or that without losing their impermeability to plasma protein they offer less resistance to the passage of water and other diffusible constituents of the plasma. In this paper we are concerned mainly with changes in permeability in the latter sense. The very low percentage of protein in samples of oedema fluid from cases of nephrosis or of the nephrotic stage of glomerulo-nephritis indicates that the natural impermeability of the limb capillaries to plasma protein is scarcely altered in these states. Increases in the permeability of the capillaries to water and crystalloids only will not CAUSE transudation of fluid, but if transudation of fluid is already determined by other factors an increase of permeability in this sense will increase the RATE of transudation. Our primary object is to compare the permeability of the capillaries to water and crystalloids in cases of hypoproteinaemia due to nephritis (or nephrosis) with the capillary permeability in health and with that in hypoproteinaemia due to a cause other than nephritis.

In subjects with equal plasma C O P's it would be possible to compare the permeability of the capillary beds of the arm by producing equal degrees of passive venous congestion in the arm artificially and comparing the rates of swelling due to oedema formation. Where the plasma C O P's are unequal the method cannot be applied in this way, for with equal heights of venous congestion the effective filtration pressure (effective filtration pressure =

capillary pressure — colloid osmotic pressure of plasma) would be greater in a subject with a lower plasma C O P. In order to equalise the effective filtration pressures a simple correction for the plasma C O P in each case was introduced. The concentration of protein in the œdema fluid from these cases is so small that the colloid osmotic pressure of the œdema fluid is negligible.

Method

The colloid osmotic pressure of the plasma is determined by Verney's technique (7) with an apparatus modified by Pickering and Wright (4)

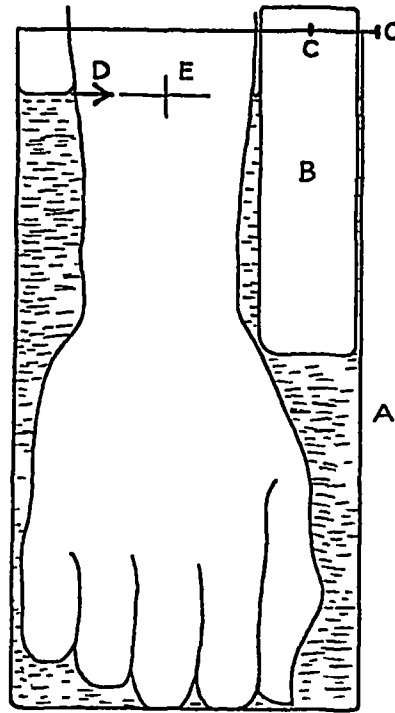


Fig. 1

The total nitrogen of the plasma is estimated by Kjeldahl's method before and after the dialysis in the osmometer and when necessary an appropriate correction for dilution of the plasma in the osmometer is made.

Sphygmomanometer cuffs are now placed round the arms of normal and hypoproteinæmic subjects. In each case the cuffs are inflated to a pressure which is equal to the measured plasma C O P of the case plus 20 cm. of water. In this way the venous pressure was raised to such a level in each experiment that the difference between the venous pressure in the arm and the plasma C O P is the same in all instances, namely 20 cm. This increased venous pressure is maintained for 5 hours and causes swelling of the arm both in the

normal and hypoproteinaemic subjects. The amount of swelling is measured by a simple device shown in Fig 1. It is composed of a glass jar A containing a removable block B which rests on the top of the jar being supported there by steel pins C C on either side of the block. A horizontal mark D is made on the jar and cross-wires E are attached to the forearm by adhesive tape and collodion. When a measurement of arm volume is to be made the arm is plunged vertically into the glass jar until the marks on the arm and on the jar are at the same horizontal level. The fingers rest on the bottom of the jar. The block B is now inserted into the jar, it serves to diminish the amount of dead space. Water at exactly 37°C is then poured into the jar until the level of the water meniscus and of the two marks are in the same horizontal plane. The volume of the jar up to the mark minus the volume of water added gives the volume of the hand and forearm up to the cross-wires. When the block B fills most of the dead space at the level of the two marks a change of 1 c c in the volume of added water causes a definite change in the level of the water meniscus.

As the arm changes from the horizontal to the vertically dependent posture which is used for measurement, gravity increases the venous pressure, hence more blood accumulates in the arm and a few minutes elapse before the volume of the arm ceases to increase. Although the additional swelling of the arm due to this change in posture was incomplete $1\frac{1}{2}$ minutes after the change in posture it was found experimentally that measurements at this time are, for comparison with similar measurements, the best. The arm volumes are determined hourly in this way for 5 hours. Except during the measurements of volume the arm is placed horizontally and at rest. With well-trained subjects the accuracy of the method is usually $\pm\frac{1}{2}\%$ of the volume of the arm up to the cross-wires.

Results

The patients investigated were 5 cases of the nephrotic type of glomerulo-nephritis with hypoproteinaemia and oedema of the legs and eyelids but not of the arms, and one case of pure nephrosis (as defined by Leiter (3)). In no case was there evidence of a recent acute exacerbation of the nephritis or of congestive heart failure.

Results showing the hourly increase in the arm volume are shown in Fig 2. The lower curve is normal in type, the upper curve shows the increased rate of swelling obtained in a case of nephritis.

The smoothness of these curves and the fact that the rate of transudation of fluid is rather less at the end of the experiment than at the outset indicate that no serious increase in the permeability of the capillaries has resulted from the venous congestion.

The total increases in arm volume expressed in c c per 100 c c of limb during the 5 hours of venous congestion are 6.6, 6.5, 6.0, 6.4, 3.6 and 5.0, average 5.7 in the normal subjects, and 15.4, 13.8, 9.0, 10.0, 11.6 and 13.8, average 12.1 in the patients with nephritis (Fig 3).

Evidently the capillary bed as a whole is more permeable in the cases of nephritis than in health, because in the same time, under similar pressure conditions it lets through more fluid

This is further emphasised by the fact that the correction we apply for the plasma C O P difference is an over correction which tends to minimise

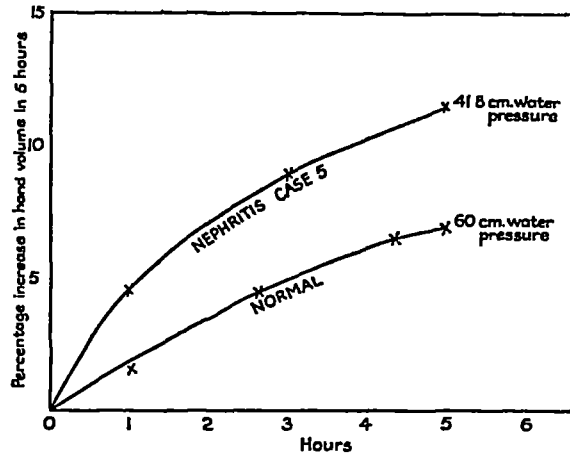


Fig 2 Rate of swelling of a hand with artificial venous congestion

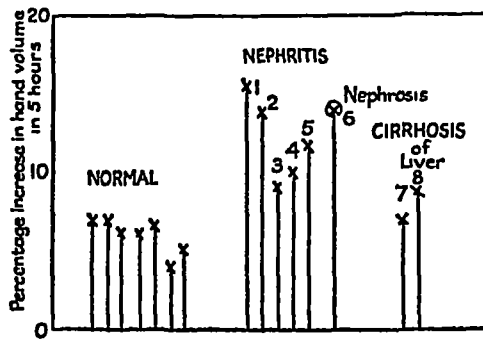


Fig 3 Rate of swelling of a hand with artificial venous congestion Each vertical line refers to a separate experiment and is marked by the case number The degree of venous congestion was equal in each case to the measured colloid osmotic pressure of the plasma + 20 cm. of water

existing differences in the rates of œdema formation Thus in attempting to secure equal effective filtration pressures we correct for the lower plasma C O P in the cases of nephritis by congesting the arms at a lower venous pressure than in the healthy controls By mechanical stretching of capillaries (and perhaps by opening up more capillaries) an increase in venous pressure is apt to increase both the surface area of the capillaries available for filtration

and their permeability. The degree of artificial venous congestion is less in the nephritic cases, consequently the surface area and permeability of the capillary bed in nephritis will not be increased so much by the artificial venous congestion as in healthy subjects.

If instead of applying a correction for the plasma C O P we apply equal degrees of venous congestion to the arms of normal and nephritic subjects, the even greater transudation rate which is then obtained in the nephritic cases measures the combined effects of a fall in plasma C O P and an increase in permeability of the capillary bed as a whole (Fig 4). As the venous pressures are equal in this experiment the mechanical effects of the venous pressure upon the capillaries are more comparable than in the previous experiment where the pressures were unequal.

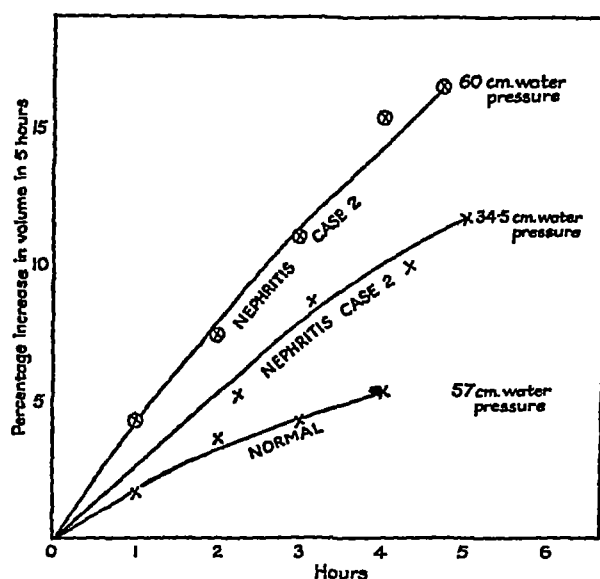


Fig 4 Rate of swelling of a hand with artificial venous congestion

As a further control two cases with hypoproteinaemia not due to nephritis were studied. These were both cases of hepatic cirrhosis with rapidly forming ascites which was tapped frequently. The great loss of protein in the ascitic fluid caused hypoproteinaemia (2) and a low plasma C O P in both subjects. The venous pressure in the arm was raised artificially in each case to a pressure equal to the measured plasma C O P plus 20 cm of water. The resulting increases in arm volume in c c per 100 c c of limb per 5 hr period are 7.0% and 10.5% of the initial volume of the arm (Fig 3). We may conclude that the permeability of the capillary bed as a whole is normal in one case and but slightly increased in the other. But the increased rate of transudation in hypoproteinaemia due to nephrosis or nephritis in the nephrotic stage is much greater. It seems therefore that

the increase in the permeability of the capillaries in the nephritic stage of glomerulo-nephritis and in nephrosis does not depend upon the hypoproteinæmia as such, but is part of the symptom complex of the nephritis

Discussion

It is clear that oedema will not develop unless the *rate* of loss of fluid from blood vessels exceeds the *rate* of absorption of the fluid by lymphatics. If there is a general increase in the permeability of vessels throughout a capillary bed, both the rates of transudation and of re-absorption through the blood vessels in that capillary bed will increase. Hence if the relationship between the capillary pressure and the plasma C O P is such that the rate of transudation from the blood vessels exceeds the rate of re-absorption of fluid by the blood vessels an increase in the permeability of the blood vessels will then increase further the rate of loss of fluid from them. In situations where the lymphatics cannot deal with this increase the tissues become oedematous.

In this investigation the sphygmomanometer cuff placed round the arm obstructs the lymphatics and prevents the drainage of fluid if the limb is at rest, so that the rate of swelling of the limb is an index of the rate of loss of fluid from the blood vessels. It has been arranged that the difference between the artificially raised venous pressure in the arm and the plasma C O P is the same, namely 20 cm of water, in the normal controls and in the hypoproteinæmic subjects with nephritis. With equal periods of congestion using the same effective filtration pressure of 20 cm of water a greater volume of fluid leaves the blood vessels in the nephritis cases than in the normal controls. It is concluded, therefore, that the capillary bed of the arm, taken as a whole, is more permeable in these subjects than in healthy controls. It seems moreover that the increased permeability is not the result of the hypoproteinæmia as such because two cases of hypoproteinæmia not due to nephritis had capillary permeabilities which were normal or but slightly increased.

The increased permeability of the blood vessels in the nephritic stage of glomerulo-nephritis is of clinical importance for it may double the rate of transudation of oedema fluid even when the transudation rate is already high because of a fall in the C O P of the plasma. Thus, a case of hepatic cirrhosis with hypoproteinæmia due to the repeated removal of ascitic fluid had a plasma C O P of 20.5 cm of water and a case of glomerulo nephritis in the nephrotic stage had a plasma C O P of 25 cm of water. The congesting pressures in the sphygmomanometer cuff were (20.5 + 20) and (25 + 20) cm of water respectively. The rates of swelling of the arms were 7% and 15.5% of the volume of the arm in 5 hours. The difference in the rates of swelling is not due to the small difference in the plasma C O P's nor to the small differences in the degrees of venous congestion and is attributed to an increase in the permeability of the capillary bed as a whole in the case of glomerulo-nephritis.

SUMMARY

A method for determining changes in the permeability of the capillary bed in the arm is described

The permeability of the capillary bed of the arm was studied in 5 cases of glomerulo-nephritis in the nephrotic stage and in 1 case of pure nephrosis in which hypoproteinaemia was associated with a measured fall in the colloid osmotic pressure of the plasma

Two cases of cirrhosis of the liver without nephritis but with hypoproteinaemia and a similar fall in the colloid osmotic pressure of the plasma were also studied

The permeability of the capillary bed was found to be considerably increased in nephritis and in the case of nephrosis and was within normal limits in the two cases of cirrhosis of the liver

It is considered that the oedema of glomerulo-nephritis in the nephrotic stage is in part due to an increase in the permeability of the capillary bed, in the sense that the passage of water and crystalloids through the capillary bed takes place more readily than in normal subjects

CASE REPORTS

Case 1 E.B., a boy of 11 years, admitted to hospital in January, 1934. His illness began two months before admission with macroscopic haematuria and oedema of the face and ankles. There was moderate lassitude but otherwise the patient felt and continued to feel well. When first seen in hospital there was oedema of the face and ankles and little or no breathlessness. The urine then contained 0.6% of albumin, a moderate number of red cells and hyaline, granular and red cell casts. The daily volume of urine passed varied but was usually about 900 c.c. The temperature fluctuated between 98° and 100° F. The left border of the heart was 1" outside the mid-clavicular line in the 4th space. The resting pulse rate varied between 72 and 100. On inspection of the neck veins there was no evidence of venous congestion and the liver was not palpable. The blood pressure was 140/100. There was 74% of haemoglobin in the whole blood.

Slight oedema of the face in the morning persisted for ten months after his admission to hospital. The degree of oedema in the ankles varied in the first four or five months but after the 5th month was either absent or trivial. Apart from the decreased tendency to oedema and a blood pressure rising gradually to 200/145 the patient's condition remained substantially the same throughout his stay in hospital. The concentrating capacity of the kidney for urea and for chloride was impaired. maximum urea percentage 1.13%, $C + \frac{U^*}{2} = 0.88$. The blood urea varied between 0.04 and 0.08%.

The capillary permeability was studied in June, 1934, the plasma C.O.P. at this time was 25 cm of water (normal 35-40 cm).

Case 2 F.A., an engineer, of 26 years, seen first in November, 1934, when he was admitted to University College Hospital. At the age of about 20 the patient noticed a tendency to puffiness of the face and at the age of 23 or 24 headaches and backaches. Oedema appeared in the legs about 14 months before and in the arms and hands about 9 months before he was seen first. Swelling of the abdomen was present occasionally. The oedema disappeared from the hands before the patient was seen in hospital.

* It has been found (Smirk) that in mild cases of nephritis the kidneys may appear to have a normal excretory function in that they are capable of forming high concentrations either of urea or of chloride in the urine, but that they differ from normal kidneys in that they are unable to form high urinary concentrations of urea and chloride at the same time. This functional difference is made the basis of a clinical test in which 13 g. of urea and 3 g. of potassium chloride are given by mouth. If U = the maximum percentage of urea in the urine after giving the urea and chloride mixture, and C = the percentage of chloride in the urine sample which contains the maximum urea percentage, then $C + \frac{U}{2}$ is greater than 2 in normal subjects and less than 2 in cases of nephritis.

On examination there were no special abnormalities apart from oedema of the face and legs and a blood pressure of 180/90 falling to 130/85 after a month in hospital. The urine contained 0.6% of protein and on microscopic examination red cells and pus. The percentage of haemoglobin in the whole blood was 82. The blood urea was 0.067% on 14/11/34 and the maximum urea concentration after giving urea was 1.6% on 15/11/34, and 2.2% on 4/12/34. The non protein nitrogen of the plasma was 0.052% on 1/12/34. The percentage of protein in the plasma was 3.4 (normal 7.5).

After three months in hospital the blood pressure was 115/75, the oedema was less and the capacity of the kidneys to concentrate urea and chloride was almost normal.

The capillary permeability was studied in December, 1934, the plasma C.O.P. at this time was 14.0 cm of water (normal 35-40 cm).

Case 3 B.W., a boy of 14 years, was seen first in April, 1934, when he was admitted to University College Hospital. The illness began with swelling of the face and legs 10 months before admission, and during this time the swelling on the face and legs gradually became more pronounced so that in the last few months before admission the facial swelling did not subside during the latter part of the day, the swelling also spread to the scalp.

Three days before admission the abdomen began to swell. Until a few days before admission the patient felt well and was able to attend school and play games though not with normal vigor. On examination, oedema of the face and legs was found together with ascites but otherwise there were no abnormal physical signs. The blood pressure was 130/98, the blood count was normal. The urine contained 0.05 to 0.1 per cent of protein, a few red cells and hyaline casts were found on microscopic examination. The maximum urea percentage after giving urea was 1.0. $C + \frac{U}{2}$ was 1.96 (normal 2.0 or more). The non protein nitrogen of the plasma was 0.015%. The percentage of protein in the plasma was 4.75.

The capillary permeability was studied a few days after the patient was admitted to hospital. Oedema of the face and feet was then present and the plasma C.O.P. at this time was 19 cm of water (normal 35-40 cm).

Case 4 A.B., an unemployed man, aged 36 years, seen first in July, 1934. The illness began in March, 1934, with tonsillitis followed by general malaise and swelling of the legs and face. The urine was then found to contain much blood and protein, the blood urea was 0.245% and the blood pressure was 175/110.

In July the condition appeared to be stationary. There was a trace of oedema in the ankles but no other abnormal physical signs. The urine contained a few red cells and 0.25% of protein. The blood urea was 0.081%. The blood pressure was 132/90.

The capillary permeability was studied a few days later and the plasma C.O.P. at this time was 27 cm of water (normal 35-40 cm).

Case 5 H.R., a bus driver of 36 years, was admitted to hospital in January, 1935. The first symptom observed two weeks before admission was oedema of the face and ankles. There was headache with blurred vision and nocturnal frequency of micturition. There was no pronounced malaise or lassitude on admission nor was there a history of either.

Physical examination revealed no special abnormality apart from oedema of the face and feet, a blood pressure of 155/120 and slight swelling of the optic discs. The urine contained much protein, red cells and casts. The percentage of haemoglobin in the whole blood was 73 on 10/2/35, and 64 on 17/3/35. The non protein nitrogen of the plasma was 0.054% on 25/1/35, and 0.071% on 17/3/35. The percentage of protein in the plasma was 4.3 (normal 7.5).

The capacity of the kidneys to concentrate urea and chloride was subnormal. maximum urea percentage 1.1, $C + \frac{U}{2} = 1.02$.

Despite the short history there was no evidence of acute renal damage. Hypoproteinaemia and a low colloid osmotic pressure of the plasma were observed from the outset, and the profuse proteinuria was accompanied by relatively few red cells. The condition was thought, therefore, to be chronic.

The capillary permeability was studied on 28/1/34, and the plasma C.O.P. at this time was 21.8 cm of water (normal 35-40 cm).

Case 6 C.W., a woman of 26, was seen first in May, 1934. The illness began about June, 1932, with lassitude, loss of weight and puffiness under the eyes in the morning. In September, 1932, there was swelling of the ankles which increased in the next few months and was associated with headache and vomiting. In July, 1933, the patient had improved to the stage of convalescence, but the symptoms and the swelling returned after a cold in September, 1933. The patient was convalescent in February, 1934, but swelling of the face, ankles and abdomen started again in March, 1934.

On examination in May, 1934, there was slight oedema of the eyelids in the morning together with marked oedema of the legs and abdominal wall and ascites. The urine contained 0.7% of

protein and hyaline and granular casts but no red cells or blood casts. The blood pressure was 95/65. Apart from this there were no physical abnormalities. The blood count and haemoglobin percentage were normal. The maximum urea percentage after giving urea was over 3% on several occasions. The non protein nitrogen of the plasma was 0.027% on 11/5/34, and 0.02% on 22/6/34, and 0.26% on 6/9/34. The percentage of protein in the plasma was 4.0 on 11/5/34, 5.05 on 22/6/34, and 5.5 on 6/9/34.

The improvement in the plasma protein percentage was due apparently to a high protein diet and to the fact that the percentage of protein in the urine had fallen to 0.1%. The plasma C O P was 19.9 cm of water on 2/6/34, and 28.6 cm of water on 9/9/34. The case appears at present to be one of pure nephrosis as defined by Leiter.

The capillary permeability was studied in September, 1934.

Case 7 C S, a brass finisher of 33 years, who was in the habit of consuming 3 or 4 pints of beer nightly. In January, 1934, the patient noticed swelling of the legs up to the knees and swelling of the abdomen.

On examination in November, 1934, slight conjunctival icterus, ascites, splenic enlargement, dilated veins on the surface of the abdomen and probably a slight decrease in the liver dulness were observed. The legs were oedematous. There were no indications of congestive heart failure or of renal disease. The urine was protein free, the blood count was normal. The Van den Bergh reaction (indirect) was positive, and the plasma contained 1.5 units of bilirubin. The ascitic fluid which was abundant and was tapped frequently contained 0.97 per cent of protein. The loss of protein in the ascitic fluid was about 6 g daily and thus caused a fall in the plasma protein and in the plasma C O P. The percentage of protein in the plasma was 5.2 on 10/12/34 and the plasma C O P was 20.5 cm of water.

The case appeared to be one of hepatic cirrhosis uncomplicated by renal disease or congestive heart failure, but with oedema which was in a large measure due to hypoproteinaemia caused by excessive losses of protein in the ascitic fluid.

The capillary permeability was studied on 10/12/34.

Case 8 A.C., a girl aged 19, was seen first in November, 1934. The general health of the patient was satisfactory throughout her illness which began in 1928 with ascites which has been tapped at frequent intervals since. The legs are swollen occasionally. In 1933 a modified Talma Morrison operation was performed and it was observed at the operation that the mesentery was much thickened.

On examination ascites and oedema of the legs and sacrum were present. The liver was 1" below the costal border (at umbilical level in 1928) and the tip of the spleen was felt in inspiration. The venous pressure in the neck was + 6 cm, but there was no dyspnoea on moderate exertion and the heart was not enlarged. Neither protein nor red cells were found in the urine.

In December, 1934, the percentage of protein in a sample of ascitic fluid was 0.8%. Hence it was calculated that protein was lost with the ascitic fluid at a rate of 3 or 4 g daily. This rate of loss of protein in the ascitic fluid is of the same order as the rates of loss of protein in the urine which are encountered in cases of glomerulo nephritis or in nephrosis. The rate of loss of protein is less than that encountered in the other case of hepatic cirrhosis (*Case 7*) and in conformity with this the plasma C O P is not so low in this patient as in *Case 7*.

It is thought that the condition is one of hepatic cirrhosis probably associated with chronic peritonitis.

The capillary permeability was studied in December, 1934, the plasma C O P at this time was 26.8 cm of water (normal 35-40 cm) and the percentage of protein in the plasma was 5.2.

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THE DIETETIC FACTOR DETERMINING THE GLUCOSE TOLERANCE AND SENSITIVITY TO INSULIN OF HEALTHY MEN

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VARIATIONS in composition of the diet have long been recognised as exerting a profound effect upon the carbohydrate tolerance of diabetic patients, but only recently has attention been directed to the effect of similar dietetic variations upon the carbohydrate tolerance of healthy people. That abstention from food lowered the sugar tolerance of normal men was clearly recognised by Claude Bernard (5) but his observations, although not actually forgotten, did not excite a sufficient degree of interest to stimulate further investigation. Following the discovery of insulin, however, the whole field of diabetic therapeutics was reconsidered, and the early recognition, by some workers, that an increase in the amount of carbohydrate and a decrease in the amount of fat in the diabetic patient's diet resulted in an improvement in his tolerance for carbohydrates, directed enquiry to the effect of similar measures on the carbohydrate tolerance of normal subjects. In 1926 Adlersberg and Porges (2) reported that a carbohydrate poor diet decreased, whilst a carbohydrate rich diet increased the sugar tolerance of healthy men, and in the following year Sweeney (12) showed that starvation and fat diets impair the normal glucose tolerance, carbohydrate diets improve it, whilst protein diets have an intermediate effect. In each of the above papers, a possible connection was suggested between the beneficial effect of a carbohydrate rich diet on the sugar tolerance and the progressive improvement shown by the successive blood sugar curves resulting from periodic doses of glucose. The latter phenomenon was originally described in 1919 by Hamman and Hirschman (6) but it is now usually referred to as the Staub-Traugott effect.

The effect of variations in diet upon insulin action has until recently received little attention. Abderhalden and Wertheimer (1) and Bainbridge (4) showed that animals were more sensitive to insulin when receiving a starchy diet than when they were receiving a fatty diet or were starving, and Tutso (13) demonstrated that the blood sugar fell more slowly in starving animals after the injection of a standard dose of insulin than in those allowed unrestricted food. Hynd and Rotter (11) more recently,

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have published results showing that there is a definite relation between the composition of the diet and the time after insulin injection when hypoglycaemic symptoms occur, animals receiving a carbohydrate diet showed symptoms earlier than animals receiving a fat diet

From a consideration of these results it appeared to me that a correlation probably existed between the effect of diet upon the sugar tolerance, and its effect upon the sensitivity of the organism to insulin. On investigation, this correlation was easily demonstrated both in men (7) (8) (10) and animals (9) and the conclusion was reached that those dietetic factors which improve sugar tolerance also increase the sensitivity to insulin, whilst those factors which impair sugar tolerance coincidentally decrease the sensitivity to insulin.

The object of the present enquiry is to determine which dietetic component is responsible for the changes in sugar tolerance and in sensitivity to insulin.

Methods

The experiments were carried out on healthy young men. Before engaging any individual, it was ascertained that he was in good health and had no history of diabetes mellitus in his family.

The subject was admitted to the ordinary hospital ward and given the diet the effect of which it was desired to investigate. All meals were prepared and weighed in the diet kitchen of the hospital,* and the consumption was checked by the ward sister. The subjects followed the ordinary routine of a hospital ward save that they were allowed to go out for walks in the morning and afternoon. At the end of seven days on any particular diet the sugar tolerance, and in some cases the insulin sensitivity, of the subject was tested, and then the next diet of the series was started. It should be noted that each particular diet was given for at least one week before the tests were performed.

On the day of the test, the subject took no breakfast and remained in bed until required. He then walked to the laboratory adjoining the ward, seated himself in a comfortable chair and rested for half an hour. The test was then started, and all the tests on all subjects were commenced within a few minutes of 10.15 a.m. During the test reading was encouraged but smoking was forbidden. Care was taken that the subject was comfortably warm. Before he was fetched from bed, the room itself was warmed and, when the tests were in progress, he was maintained comfortably warm by appropriate adjustments of clothing. No test was started until the ear was warm to the touch.

The glucose tolerance was ascertained by the effect of 50 grams of glucose on the blood sugar. The glucose was dissolved in 300 c.c. of cold water, flavoured with citric acid and essence of lemon and was

* I am indebted to Miss E. M. Marshall for the control of these diets.

taken by mouth. Before ingestion, three samples of blood were taken for the determination of the resting blood sugar level, and after the glucose had been swallowed blood samples were taken at 10 minute intervals for three hours. The taking of samples was timed by a stop watch to the nearest quarter minute.

The sensitivity to insulin was determined by the effect of the intravenous injection of 3 units of crystalline insulin solution*. Before the injection, four blood samples were taken to ascertain the level of the resting blood sugar, and after the injections samples were obtained first at 1½ minute and later at 2 minute intervals.

The blood sugar estimations were carried out by the Hagedorn-Jensen method on 0.1 c.c. of whole blood. The blood samples were taken directly into the pipette from the freely flowing blood from a puncture of the lobe of the ear. The details of the actual technique for obtaining reliable samples of capillary blood have been described elsewhere (8), and it will suffice here to indicate the degree of accuracy attained. A subject was taken who was habituated to the technique of the sugar tolerance curve. He was prepared in the usual way and was under the impression that he was to undergo the ordinary test. But instead of a solution of 50 grams of glucose, he was given to drink a similarly flavoured solution of saccharine, and samples were taken in the usual way for 90 minutes. The result is shown in the lowest curve in Fig. 1. In twelve separate samples the blood sugar level varied only from 97 to 100 mg/100 c.c. It is justifiable, therefore, to regard variations in the blood sugar level of more than 4 mg/100 c.c. as significant of an actual change in the sugar content of the blood.

Extraneous factors influencing the sugar tolerance and sensitivity to insulin are theoretically many but in this investigation there are only two such factors liable to produce erroneous results. The first is the chance occurrence of intercurrent infections, and the second is through the subject not adhering to the diet.

Infection impairs sugar tolerance and insulin sensitivity, and on more than one occasion detection of this impairment has resulted in the discovery that the subject had an infection. For example, one subject who showed an unexpected impairment of tolerance admitted that he had toothache during the test and twenty-four hours later he had developed all the physical signs of an alveolar abscess. The rule adopted in these cases was, if infection were discovered to discard the experiment and to repeat the test later when the subject's health was undoubtedly normal, but if no signs or symptoms of infection could be elicited, the test was accepted. It is surprising how difficult it is to keep a normal person free from mild infection for several weeks in a hospital ward.

* I am indebted to Dr J. W. Trevan of the Wellcome Physiological Research Laboratories for a sterile solution of crystalline insulin assayed at 10 units per c.c.

As far as could be ascertained, all the subjects adhered to the diet. Its consumption being checked, the only possibility of error lay in the surreptitious supplementing of the diet. To some extent such a possibility was detectable. On the least palatable diet, that containing little carbohydrate and much fat, ketonuria occurred, and this was tested for in all the urine specimens passed. The eating of extra carbohydrate, whilst this diet was being taken, was known to result in a sudden disappearance of the ketonuria, but no such disappearance ever occurred in the urines of our subjects. If the unpalatable diet were adhered to, it is probable that the more palatable diets were not broken.

The comparison of blood sugar tolerance curves and insulin depression curves

No satisfactory method has hitherto been proposed for comparing different blood sugar tolerance curves. Some authorities take as their criterion the height of the peak of the curve, others the time after glucose ingestion that the peak occurs, and yet others the time required for the blood sugar to fall back to within certain arbitrary "normal" limits. These criteria are demonstrably unsound. If a series of curves is obtained, each curve under exactly the same conditions from the same individual, it will be found that great variations occur in the height and time of the peak, and considerable variation in the time of return of the blood sugar to "normal" levels. Of these three criteria, the latter is the most reliable but none are sufficiently accurate for the present purpose. A new method of comparison was, therefore, sought, and on the basis of various theoretical considerations, a criterion was elicited which proved satisfactory. The criterion was the area enclosed by the blood sugar curve above the resting level from which it started.

A reference to Figs 1, 2, 3 and 6 will show that there is a great variation in the time taken by the different blood sugar curves to return to the resting level. It was necessary, therefore, to decide at what time the curves should be terminated so that the areas traced out up to this point could be compared. The time chosen was the shortest time taken by any curve of the series to return to the resting level. This time would appear to offer a more natural point of termination for comparison of the curves than an arbitrary time limit chosen by the investigator. All the other curves were, therefore, cut short at this time and comparison made between the areas thus demarcated. For example, in Fig 2, the earliest time that any curve in this series returns to the resting level is at 108 minutes. A vertical line is drawn at this point to cut the other curves of the series and the areas compared are those bounded above by the blood sugar curve up to the point where it is cut by the vertical line, below by the resting blood sugar level up to the vertical line, and to the right by the vertical line from the point of section by the blood sugar curve to its rectangular junction with the resting blood sugar line. The same method of comparison is exemplified in Figs 4 and 6.

The areas thus measured are expressed in "milligramme-minutes" (mg /mins)

TABLE I

Table showing constancy of the area demarcated by the sugar tolerance curve when a constant diet is being taken

Subject	Diet				Area of glucose tolerance in mg /mins
	No	Carb	Prot	Fat	
M	1	55	88	202	11,960
	2	"			13 690
	3	660	90	42	5,590
	4	"	"	"	5,400
B	1	55	90	160	11,930
	2	,	"	"	10 660
	3	660	90	42	4,160
	4	"	"	"	4,550
C	1	56	87	255	10,890
	2	"	"	"	11,100
	3	"	"	,	10,750

Subject M The curves were taken at consecutive intervals of ten days

Subject B Curves 1 and 3 were separated by an interval of one week. The subject then left hospital for ten days. One week after his return curve 2 was obtained and one week after this curve 4

Subject C Curves 1 and 2 were separated by one week. Curve 3 was obtained after the subject had taken the same diet for the week following his return to hospital after an absence of six weeks

Subjects M, B and C were not used in the investigation reported in this paper but data obtained from them in a previous series of experiments were used to construct the above table

When this method of comparison was deduced data were available from previous experiments which permitted its application. The results are shown in Table I. It will be seen that for the same subject taking the same diet the areas of separate sugar tolerance curves measured in the above manner are remarkably constant. It is worthy of note that none of the curves shown in Table I were taken in daily sequence, and indeed, some were separated by intervals as long as six weeks. With the more expert technique used in the series of experiments in the present

paper, the constancy is even more remarkable, as can be seen in Table VI. On the strength of these results the method of comparison by areas was adopted.

The comparison of the insulin depression curves was made in a similar way. The time originally chosen at which the area traced out should be marked off was the time at which the blood sugar commenced to return to normal. In the experiments in which this time could be taken the results showed good correspondence, but for the following reason this time limit could not be applied to all cases. With the small doses of insulin used, the curve of depression of the blood sugar from the resting level to the depth of the hypoglycæmic trough is not always a smooth sweep down—often it is interrupted by many small elevations so that the curve oscillates. In these cases the position of the maximum depth of the trough is not easy to determine. It was, therefore, thought advisable in such cases to take an arbitrary line which terminated the insulin curves at a point where they were still smooth. Fig 7 shows a series of insulin depression curves from Subject I all terminating at 15 minutes after the intravenous injection of insulin. Such curves are demarcated above by the line of the resting blood sugar level, to the right by the vertical line at 15 minutes dropped to cut the blood sugar depression curve, and below by the blood sugar depression curve itself.

Termination of the curve at an arbitrary time limit is undoubtedly artificial and it is not surprising that the areas thus obtained evince discrepancies on comparison. But these discrepancies are slight and do not affect the significance of the comparison. In those insulin depression curves in which the termination time can be decided naturally as the time at which the blood sugar commences to return to normal levels, such discrepancies almost disappear, so that in any particular subject the insulin depression area remains practically constant if the experimental conditions remain unaltered. For example, in one subject on a fixed diet the insulin depression area on two occasions, separated by an interval of one week, was 366 and 380 mg /mins. It may, therefore, be concluded that the method of expressing insulin depression curves in terms of the areas demarcated yields data which are capable of accurate comparison.

The absolute value of the areas traced out in different subjects by the individual curves obtained on the same diet varies greatly. Each individual appears to have his own characteristic area for a particular diet. For this reason only curves obtained on the same subject may be compared.

To obtain the areas, the blood sugar values were charted and the points connected by smooth curves. French drawing curves being used for the purpose. A consideration of the figures in this paper will show that the rise and fall of the blood sugar occurs in a smooth manner and justifies the connection of the points by curves rather than straight lines. The curve being charted, the area to be taken into consideration was

demarcated in the manner described, and then measured by means of a planimeter

RESULTS

The influence of the composition of the diet on the glucose tolerance

In Fig 1 are shown two glucose tolerance curves from the same individual. The upper curve (glucose curve, Diet 1) indicates subnormal tolerance and was obtained when the subject was taking a low-carbohydrate high-fat diet, the lower curve (glucose curve, Diet 7) indicates supranormal tolerance and was obtained when a high-carbohydrate low-fat diet was being taken. The object of the first part of the investigation was to detect the particular dietary factor responsible for this change in tolerance.

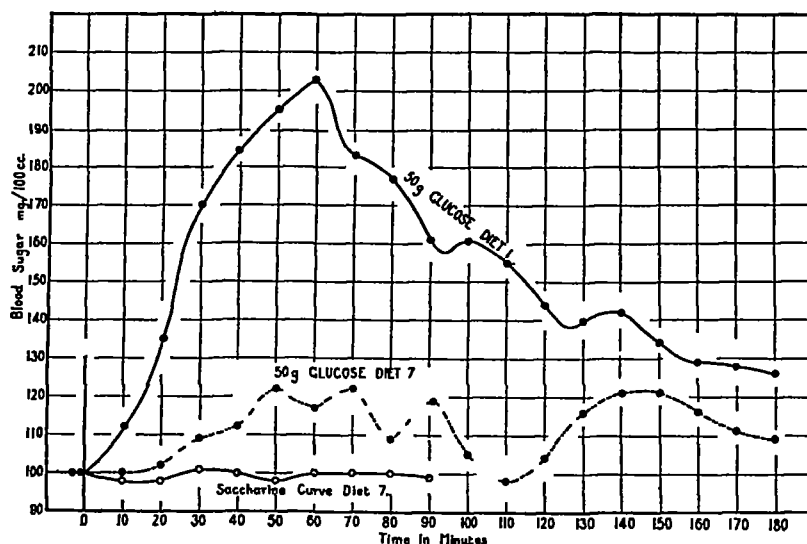


Fig 1 Three blood sugar curves from subject I. The curve on Diet 1 shows the effect of a low-carbohydrate high fat diet on the glucose tolerance curve produced by oral administration of 50 g of glucose, the curve on Diet 7 shows the effect of a high carbohydrate low fat diet. The saccharine curve shows that no rise of blood sugar occurs after drinking a solution of saccharine and also demonstrates the accuracy with which blood sugar estimations were made.

Five possibilities present themselves. The determining factor may be either a change in the calory value, or the amount of protein, or the amount of carbohydrate, or the amount of fat, or the ratio of fat to carbohydrate in the diet. The first set of experiments was devised to determine whether the calory value or the amount of protein in the diet influence the tolerance. To this end a series of seven diets was constructed as shown in Table II. The amount of protein and the

calory value of the diet were maintained constant throughout the series, but the composition of the diets ranged from a low-carbohydrate high-fat diet (Diet 1) to a high-carbohydrate low-fat (Diet 7) Proceeding

TABLE II DIETS (SERIES 1)

Diet No	Composition			Calories
	Carb	Prot	Fat	
1	50	80	240	2,680
2	125	80	207	2,680
3	200	80	173	2,680
4	275	80	140	2,680
5	350	80	107	2,680
6	425	80	73	2,680
7	500	80	40	2,680

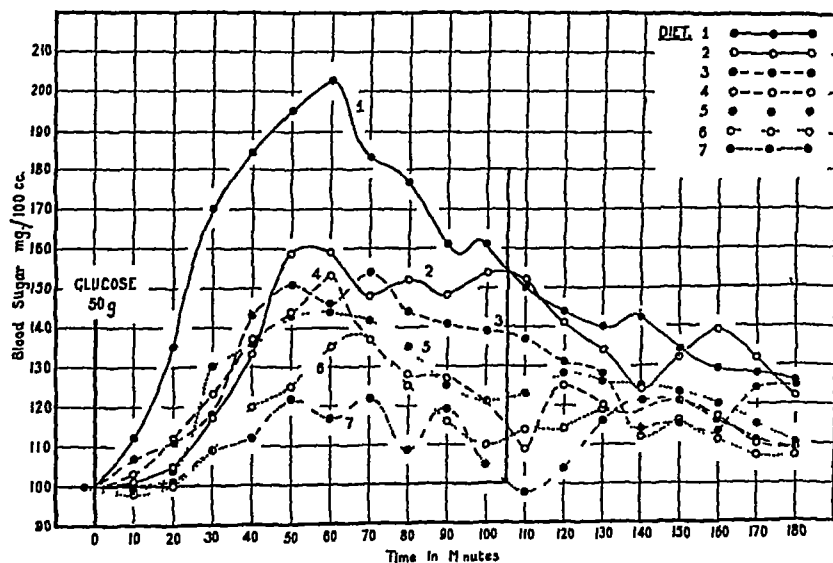


Fig 2 The seven glucose tolerance curves produced in subject I as a result of giving the seven diets in Table II

from Diet 1 to Diet 7 each diet of the sequence differed from the preceding one by an increment of 75 g of carbohydrate and a decrement of 33 g of fat, so that in consecutive curves the carbohydrate increases whilst the fat decreases

This series of diets was tested on three normal subjects. Subject I received each of the seven diets on consecutive weeks but subjects II and III were given only Diets 1, 3, 5 and 6. Fig 2 shows the series of tolerance curves from subject I and Fig 3 the series from subject III. Table III gives the areas for the three subjects marked out by the glucose

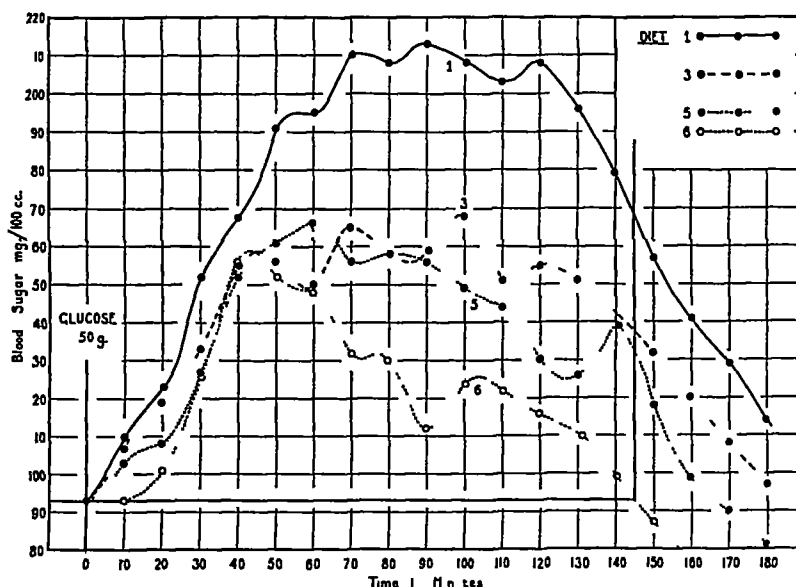


Fig 3 The glucose tolerance curves of subject III obtained when Diets Nos 1, 3, 5 and 6 of Table II were given

TABLE III

Table showing the effect on the glucose, in three normal subjects, of giving the diets of Table II

Diet No	Area of glucose tolerance curve in mg /mins		
	Subject I	Subject II	Subject III
1	6,833	*8,730 (?)	12,510
2	3,785	—	—
3	3,560	6,860	7,620
4	2,850	—	—
5	2,767	6,125	6,715
6	1,815	4,850	4,130
7	1,136	—	—

* The curve corresponding to Diet 1 was, in this subject, technically unsatisfactory. For this reason in calculating the points for Fig 8 the tolerance area for Diet 1 has been calculated from the tolerance area on Diet 3 as 11,250 mg /mins

tolerance curve corresponding to each diet and in Fig 4 the effect of this sequence of diets on the tolerance is demonstrated more clearly by plotting the respective tolerance areas (ordinate) against the carbohydrate content of the diet (abscissa). The area, of course, might equally well have been charted against the fat content of the diet or the fat-carbohydrate ratio of the diet

The results shown in Figs 2, 3 and 4, and in Table III show that, despite the fact that the protein content and calory value of each diet of the series have been maintained constant, the glucose tolerance curves

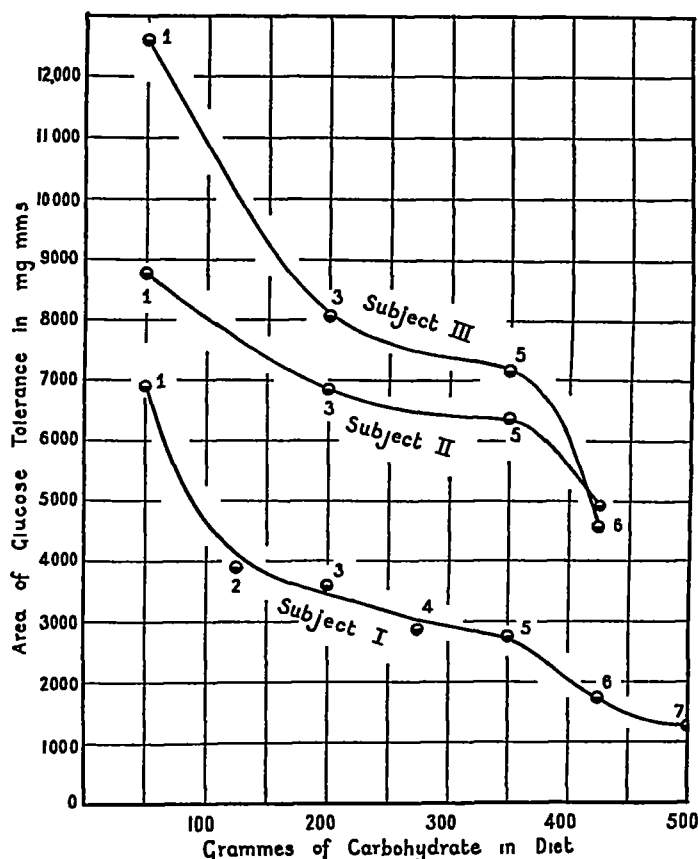


Fig 4 Curves showing the relationship between the glucose tolerance area and the composition of the diet in subjects I, II and III as determined by giving the diets of series 1 (Table II)

show the characteristic improvement as the diet changes from a low-carbohydrate high-fat diet to a high-carbohydrate low-fat diet. The factor determining glucose tolerance is, therefore, neither the protein content nor the calory value of the diet.

Three possibilities now remain to explain the improvement in tolerance on this series of diets. The determining factor may be either the increase

in the carbohydrate content, or the decrease in the fat content or the change in the fat-carbohydrate ratio of the diet. The decision as to which of these three possibilities is the determining factor was revealed by investigating the effect of the fat-carbohydrate ratio.

Two series of diets were now devised in each of which the fat-carbohydrate ratio was kept constant. In both the protein was also maintained constant. In series 1A (Table IV) the fat-carbohydrate ratio

TABLE IV DIETS (SERIES 1A)

Table showing the diets used in the proof that the glucose tolerance improves as the diet changes from a low-carbohydrate high fat diet to a high carbohydrate low fat diet even if the ratio of calories derived from fat remains constant

Diet No	Composition			Calories	Ratio fat calories carb calories	Area of glucose tolerance curve (mg /mins)
	Carb	Prot	Fat			
1a	100	80	87	1,500	1.96	7,050
2a	150	80	132	2,100	1.96	5,505
3a	200	80	173	2,680	1.96	4,470
4a	300	80	260	3,860	1.96	3,460

was high, i.e., the diets approximated to the low-carbohydrate high-fat type, whilst in series 1B (Table V) the ratio was low, the diets approximating

TABLE V DIETS (SERIES 1B)

Table showing the diets used in the proof that the glucose tolerance improves as the diet changes from a low carbohydrate high fat diet to a high-carbohydrate low fat diet even if the ratio of calories derived from fat remains constant

Diet No	Composition			Calories	Ratio fat calories carb calories	Area of glucose tolerance curve (mg/mins)
	Carb	Prot	Fat			
1b	313	80	92	2,400	0.68	4,430
2b	437	80	128	3,200	0.68	4,170
3b	555	80	163	4,000	0.68	2,595

to the high-carbohydrate low-fat type. Each series formed a sequence so that each consecutive diet differed from its predecessor by the addition both of a definite amount of carbohydrates and of the equicaloric amount of fat required to keep the ratio constant. Subject IV received series 1A, subject V series 1B. If the fat-carbohydrate ratio is the determining

factor then it being maintained constant the sugar tolerance should remain constant in each series of diets. The right-hand column in Table IV gives the glucose tolerance areas obtained from subject IV, when taking the diets in series 1A, whilst the corresponding column in Table V shows the tolerance areas found in subject V when the diets of series 1B were given. In Fig 5 these areas are charted against the carbohydrate content of the diet.

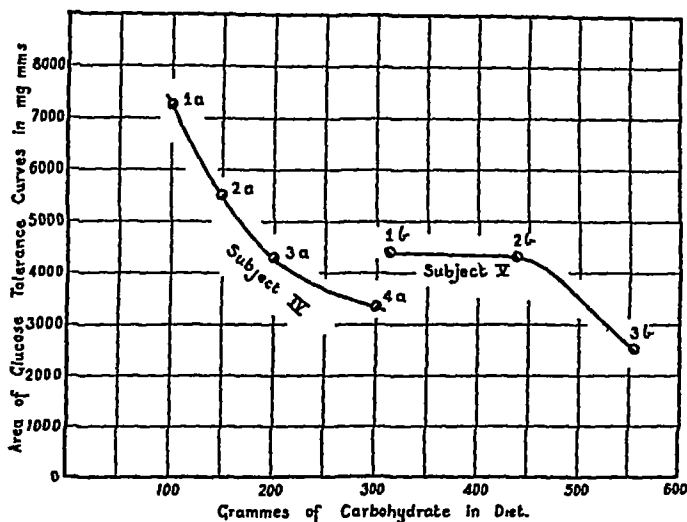


Fig 5 Two curves showing the relationship between the glucose tolerance area and the amount of dietary carbohydrate in subjects IV and V when the series of diets given had a constant fat calories/carbohydrate calories ratio (Tables IV and V)

It will be seen on comparing Figs 4 and 5 that the tolerance improves in the same manner as in the previous set of experiments although the fat-carbohydrate ratio has been kept constant. The fat-carbohydrate ratio thus has no influence on the sugar tolerance. The decision between the two remaining possibilities can be made from the data already available.

The first set of experiments (Figs 2, 3 and 4, and Table II) had permitted the conclusion that three possibilities remained. Of these three possibilities only two now remain for consideration. Either the determining factor is the increase of carbohydrate in the diet or the decrease of fat in the diet. In the series of Diets 1A and 1B, not only the carbohydrate but the fat increased in each diet and yet despite the increasing fat content the tolerance improved on each successive diet. Decrease in the amount of fat thus cannot be the factor determining the improving tolerance in the first set of experiments. The increase in the absolute amount of carbohydrate in the diet is the only factor common to both sets of experiments and this, therefore, must be the determining factor.

This conclusion may be put to a crucial test. If a series of diets is constructed with constant carbohydrate but increasing fat content then if the above conclusion is correct the tolerance should be exactly the same on each diet of this series. Such a series is shown in Table VI (series 1c). The tolerance curves for these three diets are shown in Fig. 6.

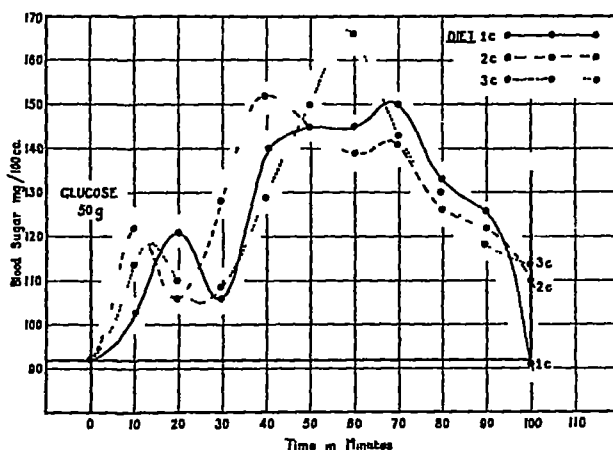


Fig. 6 Three curves from subject IV showing that if the carbohydrate content of the diet is kept constant then, despite progressive increase in the fat, the glucose tolerance also remains constant (see Table VI).

and the tolerance areas are given in the right-hand column of Table VI. It will be seen that the sugar tolerance is exactly the same on each of the three different diets.

TABLE VI DIETS (SERIES 1c)

Table showing that the glucose tolerance area remains constant despite changes in the fat content of the diet provided that the carbohydrate content of the diet is maintained constant.

Diet No	Composition			Calories	Area of glucose tolerance curve (mg/mins)
	Carb	Prot	Fat		
1c	250	80	100	2,220	3,500
2c	250	80	200	3,120	3,527
3c	250	80	300	4,020	3,534

The results of this investigation may thus be summarised in the conclusion that the sugar tolerance of a healthy individual is determined solely by the carbohydrate content of the diet received.

The influence of the composition of the diet on the sensitivity to insulin

It has been stressed in previous papers (7) (8) (9) (10) that those diets which improve the sugar tolerance simultaneously increase the sensitivity of the organism to insulin, and that those diets which impair sugar tolerance similarly decrease the sensitivity to insulin. The proof, which has just been given, that the amount of carbohydrate in the diet is the sole factor determining the sugar tolerance of a healthy individual suggests, therefore, that variations in the amount of dietary carbohydrate may have a significant effect upon the healthy individual's sensitivity to insulin. On investigation this suggestion was found to be justified.

In judging variations in insulin sensitivity the significance of two factors in the insulin depression curve should be appreciated. The first is the length of time after the intravenous injection of insulin before any fall in blood sugar is detectable—this I have referred to as the latent period (7) (8) (9) (10). The second is the rate of fall of blood sugar after

TABLE VII.

Table showing the effect of increasing the dietary carbohydrate on the latent period and the insulin depression area of subject I. The diets are the same as in Table II.

No	Diet			Latent period mins	Area of insulin depression curve mg/mins
	Carb	Prot	Fat		
1	50	80	240	7	30
2	125	80	207	6	54
3	200	80	173	4-5	97
4	275	80	140	4	119
5	350	80	107	3-4	130
6	425	80	73	2	152
7	500	80	40	2	154

the fall has commenced. It is important to realise that in a subject receiving a constant diet the length of the latent period is independent of the dose of insulin and secondly that above a certain maximum dose of insulin, about 5 units, the rate of fall of the blood sugar also is independent of the dosage. The only factor which can alter either the latent period or the rate of fall is change in the sensitivity of the subject to insulin (8) (9) (10). For doses of insulin below 5 units the rate of depression of the blood sugar is not maximal but with the same dose of insulin the rate remains constant provided the composition of the diet is also maintained constant. Now the length of the latent period and the rate at which the blood sugar falls up to a fixed point in time

determine the area enclosed by the depression curve below the resting level. The activity of a standard dose of insulin in an individual may thus be expressed quantitatively by the insulin depression area and as the latent period and the rate of fall remain constant if the diet is fixed then naturally the area remains constant. For example in one subject on a fixed diet the insulin depression area on two occasions, separated

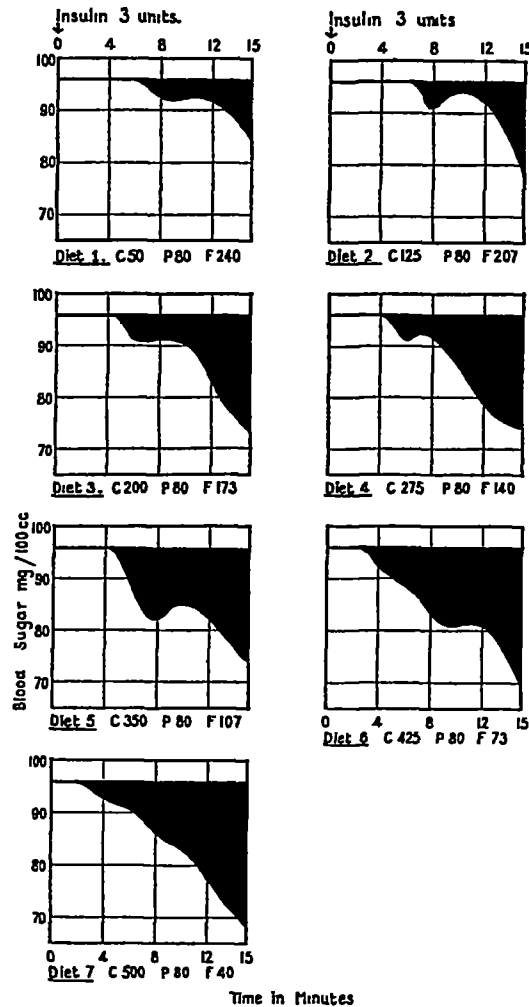


Fig 7 Seven insulin depression curves, after injection of 3 units of crystalline insulin solution intravenously, obtained from subject I by giving Diets Nos 1 to 7 of Table II

by an interval of one week, was 366 and 380 mg /mins. Further examples of this constancy can be found, if required, in my papers referred to above. Thus if a subject is given a series of diets of varying composition and,

on each, his insulin sensitivity is tested by the response to a standard dose of insulin, change in the duration of the latent period and change in the rate of depression will reveal change in insulin sensitivity, and this may be expressed quantitatively by comparing the different insulin depression areas. The relation of insulin sensitivity to changes in dietary composition was tested on subject I. This subject was given the series of diets shown in Table II and at the end of each week an insulin depression curve was obtained, and next day a sugar tolerance curve. In this series of diets it will be remembered that the protein content and calory value of each diet is maintained constant whilst in each succeeding diet the carbohydrate content is increased by a constant increment whilst the fat content is decreased by equicaloric decrement. The results from this set of experiments are shown in Table VII and in Figs 7 and 9.

Table 7 shows that the latent period shortens, and the insulin depression area increases as the carbohydrate content of the diet increases. In Fig 7 it can also be seen that with the shortening latent period the rate of depression of the blood sugar increases. The correlation between change in the amount of carbohydrate in the diet and change in the individual's insulin sensitivity is expressed as a curve in Fig 9 by charting the insulin depression areas against the carbohydrate content of the corresponding diet.

It may, therefore, be concluded that the sensitivity to insulin of a healthy individual is determined by the carbohydrate content of the diet.

NOTE.—The seven insulin depression curves obtained on subject I were not altogether satisfactory. The first experiment passed off smoothly until hypoglycæmic symptoms set in. The subject then fainted, apparently from sheer surprise. This had the unfortunate effect in the second experiment (curve on Diet 2, Fig 7) of rendering the subject extremely apprehensive and I am of the opinion that the surprisingly small fall of blood sugar obtained in this test may largely be explained by the subject's extreme nervousness. However, the third experiment passed off without untoward event and in the remaining four investigations the subject was quite nonchalant and read a newspaper the whole time. But apart from these accidents there is another ground for dissatisfaction. In this series the fall of blood sugar was never smooth but always somewhat irregular and with such curves the areas cannot be compared with the same degree of accuracy as when the fall of the curve is smooth.

DISCUSSION

The relation between the carbohydrate content of the diet and the area of the glucose tolerance curve

The preceding results demonstrate that the glucose tolerance of a healthy individual is determined solely by the carbohydrate content of the diet received and it would appear profitable, in view of the decisive nature of this demonstration, to enquire further into this relationship. Fig 4 shows that, in each of the three subjects, the curve expressing the relationship between the carbohydrate content of the diet and the glucose tolerance area, is of the same type. It is S shaped in form. As the amount of dietary carbohydrate is increased from 50 g to about 150 g there is a steep fall in the curve indicating a marked improvement in tolerance, with further increase of carbohydrate from 150 g to 350 g

the curve becomes almost horizontal as improvement in tolerance is relatively slight, but then, when the carbohydrate is raised from 350 g to about 450 g, a second sharp fall in the curve occurs as the tolerance shows a second phase of well-defined improvement. That this form of curve is not an artefact dependent on a particular sequence of diets is shown by Fig 5. Here are shown two half curves, from two different subjects, resulting from diets differing considerably from the first series.

The curve for subject IV was obtained from the tolerance on diets containing between 100 g and 300 g of carbohydrate and is in every respect similar to that part of the curves in Fig 4 for the same carbohydrate range. The curve for subject V resulted from diets ranging from 313 g to 555 g of carbohydrate and this again corresponds in form to that portion of the curves in Fig 4 dependent on the same changes in dietary carbohydrate. This latter curve is of especial importance as it negates the suggestion that the great improvement in tolerance found in the other subjects when the dietary carbohydrate was increased from 50 g to 150 g can be explained in part, by the presence of initial nervousness adversely affecting the first tolerance curve and the absence of nervousness producing a disproportionately good result in the second curve. If this contention were correct then the factor of nervousness should produce a noticeable difference between the first and second curves taken on a series of diets the first and second diets of which had a carbohydrate content corresponding to the horizontal part of the curves in Fig 4. Subject V was given such a series of diets and it will be seen from Fig 5 that the first and second tolerance areas lie on a practically horizontal line. The form of the curve shown in Fig 4 is, therefore, not an artefact but a real expression of the relationship of two variables. For convenience the term "Determination curve of glucose tolerance" is proposed for these curves.

The similarity in form between the determination curves of glucose tolerance for all five subjects is suggestive that a common basis of expression might be found for all curves in such form that one curve might be constructed which would express for all healthy subjects the relationship between glucose tolerance and dietary carbohydrate.

The first attempt to achieve this object was made by expressing the tolerance areas obtained on the different diets in ratio to the tolerance area obtained on the diet containing 50 g of carbohydrate. This ratio, $\frac{\text{tolerance area on } X \text{ g of carbohydrate}}{\text{tolerance area on 50 g of carbohydrate}}$ where X is any fixed amount of carbohydrate, was speedily found to vary greatly in different subjects, and it was soon realised that the data available did not permit the expression of the areas in different subjects as any function of the absolute area. It appears that each subject has his own characteristic tolerance area corresponding to each definite amount of carbohydrate, and that although the tolerance areas is constant in each subject for

Area on diet containing 200 g carbohydrate = 3,560 mg /mins

Change in area from

area on diet ,, 50 g ,, = - 3,273 mg /mins

$$\text{Percentage change} = \frac{-3,273}{-5,018} \times 100 = 65\%$$

Expressing the results obtained in subjects I, II and III in this manner and plotting these percentage changes in tolerance against the corresponding amounts of dietary carbohydrate the curve shown in Fig 8 was obtained. Although it is obvious that this curve is far from exact, it probably gives a tolerably good idea of the general relationship between change in glucose tolerance and change in carbohydrate content of the diet. This contention derives considerable support from the fact that it is possible by means of this general glucose-tolerance determination curve to calculate the percentage change in tolerance found in the two subjects IV and V who were not submitted to the full range of dietary change from 50 g to 425 g of carbohydrate (Tables IV and V, and Fig 5).

Thus, for example, in subject IV the dietary carbohydrate was as follows: 1st diet 100 g, 2nd diet 150 g, 3rd diet 200 g, 4th diet 300 g. From the curve 100 g carbohydrate corresponds to 48% improvement in tolerance from 50g carbohydrate

,, ,, 150 g ,, ,, ,, 60% improvement in tolerance from 50g carbohydrate

% change in tolerance between 100 g and 150 g = 12%

In subject IV change in area between 100 g and 150 g = 1,545 mg /mins

1% change in tolerance corresponds to $\frac{1,545}{12}$ mg /mins change in area

= 128.7 mg /mins change in area

In subject IV change in area between 100 g and 200 g = 2,580

,, ,, ,, ,, ,, ,, = $\frac{2,580}{128.7}\%$ = 20%

i.e., percentage change in tolerance corresponding to change in the carbohydrate quantity of the diet from 50 g to 200 g = 48% + 20% = 68% and according to the curve of Fig 8, a diet of 200 g carbohydrate corresponds to 65% improvement in tolerance. This correspondence in results demonstrates that the general determination curve of glucose tolerance is sufficiently exact to permit the prediction with some degree of accuracy of the change in sugar tolerance which will occur as a result of a change in the amount of dietary carbohydrate.

There are not sufficient data as yet to permit conjecture as to the general significance of the form of the curve, but comment may be made

on one part of it As the amount of carbohydrate presented to the body for metabolism falls below 100 g per day the tolerance rapidly declines The shape of the curve in this region suggests that it will run to asymptote along the ordinate, so that a comparatively small decrease below 50 g of the amount of carbohydrate utilized in the body will result in a great decrease in tolerance and the glucose tolerance curve will become frankly diabetic in type The high and prolonged blood sugar tolerance curve of the diabetic may thus be explained on the grounds of the deficient utilization of carbohydrate by these patients It will further be noticed that the decrease of carbohydrate utilization required to change the relatively impaired normal tolerance corresponding to 50 g of dietary carbohydrate into the grossly impaired tolerance of the diabetic is surprisingly small In view of this observation an explanation of the sudden onset of diabetic symptoms may be deduced from the curve If in a given individual the utilization of carbohydrate is becoming restricted at a uniform rate, the subject will be unaware of anything amiss until the utilization falls below the amount corresponding to an intake of 50 g of exogenous carbohydrate each day From this point onwards, although the utilization of carbohydrate may continue to be restricted at the same uniform rate, the tolerance will show rapidly progressing impairment Pathological hyperglycæmia and glycosuria will ensue relatively suddenly with the consequent sudden appearance of the dependent symptoms of thirst and polyuria It appears, therefore, that the division between diabetic and normal sugar tolerance is a great deal narrower than has been suspected, and that sudden appearance of symptoms of diabetes mellitus in man does not necessarily indicate an exacerbation of the disease processes

The correlation between change in glucose tolerance and change in insulin sensitivity

Experiments have been presented which show that there is a definite relationship between the composition of the diet and the sensitivity of an individual to insulin, and in Fig 9 this relationship has been expressed as a curve by charting the insulin depression areas for subject I against the carbohydrate content of the corresponding diets This curve may be termed the "Determination curve of insulin sensitivity" and it will be seen it is of the same shape as the determination curve of glucose tolerance The two curves, however, have an opposite direction, so that whilst the determination curve of insulin sensitivity has its concavity directed towards the abscissa, the determination curve of glucose tolerance has its convexity in this direction Obviously this results because improvement in glucose tolerance is shown by decrease in area whilst improvement in insulin sensitivity manifests itself as increase in area

In the previous section it has been shown that by expressing the changes in glucose tolerance area, not as absolute units, but as percentage

change in area, it is possible to reduce the determination curves of glucose tolerance for all subjects to a common basis and obtain one curve expressing, for normal individuals, the relationship between change in glucose tolerance and change in the composition of the diet. In exactly the same way any change in the area of the insulin depression curve may be expressed as a percentage of the total change and a curve constructed which will express, for all healthy subjects, the relation between change in insulin sensitivity and change in composition of the diet. The general determination curve of insulin sensitivity thus constructed is in every way the same as the general determination curve of glucose tolerance in Fig 8

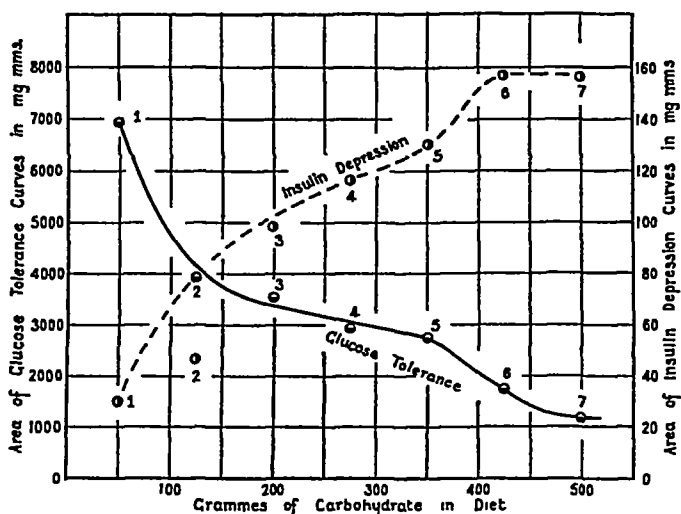


Fig 9 The determination curve of glucose tolerance and the determination curve of insulin sensitivity for subject I determined by giving the series of diets in Table II

The exact agreement of these two curves indicates that there is a definite correlation between change in insulin sensitivity and change in glucose tolerance and this view is further strengthened by a consideration of Fig 9 in which are charted both the glucose tolerance and the insulin sensitivity curves for the same subject. The correlation is expressed in Fig 10 where the percentage improvement in glucose tolerance is charted against the percentage improvement in insulin sensitivity for the corresponding diet. The points thus derived fall approximately on a straight line inclined at an angle of 45° to the abscissa.

Data from three normal subjects have been used in the construction of Fig 10, and different doses of insulin have been taken as the standard dose in each. Thus in subject I the insulin dose was 3 units, in subject M 5 units, and in subject C $2\frac{1}{2}$ units. Yet the points from all three subjects

fall on the same straight line. It appears, therefore, that change in diet produces the same percentage change in insulin sensitivity whatever the standard amount of insulin taken as the test dose. The conclusion is thus reached that change in insulin sensitivity consequent upon change in the amount of dietary carbohydrate is independent of the dose of insulin.

The significance of this conclusion is clarified by the consideration of some results which have already been published (8). These show that

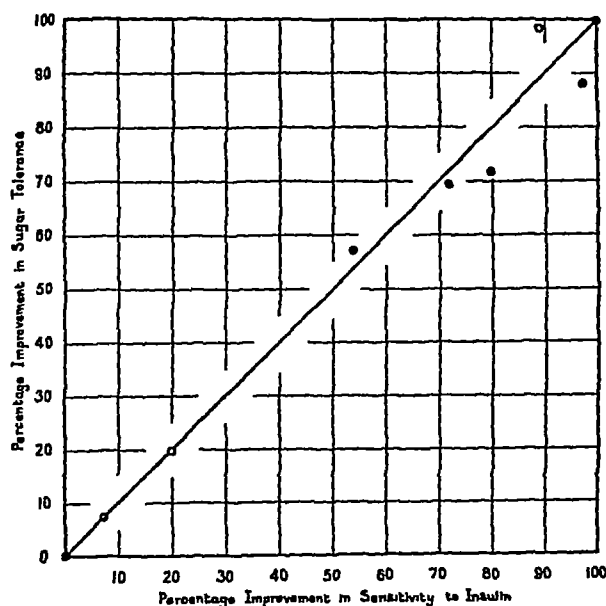


Fig 10 Chart showing the relationship between improvement in glucose tolerance and improvement in insulin sensitivity. The discs show the points derived from experiments on subject I in which 3 units of insulin was used as the standard dose, the circles, the two points available from the data on subject M in which 5 units was the standard dose, and the half circle—half-disc, one point available from subject C in which $2\frac{1}{2}$ units of insulin was the standard dose used. The point corresponding to the erroneous insulin depression curve obtained on Diet 2 from subject I is omitted.

above a certain maximum dose of insulin, which is about 5 units, increase in the insulin dose produces neither a shortening of the latent period during which the blood sugar remains constant after injection, nor an acceleration of the fall of blood sugar once it has commenced. Larger doses merely increase the length of time that the blood sugar is maintained at low levels. With doses below 5 units of insulin, increase of dosage up to the 5 unit maximum results in acceleration of the rate of fall of the blood sugar and possibly shortens slightly the latent period, but for any particular constant dose a subject receiving a diet containing a standard amount of carbohydrate shows always a latent period of the

same time and a depression of the blood sugar of the same rate. One factor only is capable either of shortening the latent period or accelerating the rate of blood sugar fall. This factor is the sensitivity of the organism to insulin. It is determined by the amount of carbohydrate in the diet and its development is independent of the dose of insulin used. It is thus manifest that the efficiency of insulin in a particular individual is governed by the independent factor of sensitivity to insulin, and that to this factor must be assigned a role of considerable significance in carbohydrate metabolism.

The question now arises as to the accuracy with which the straight line in Fig. 10 expressed the relationship between change in insulin sensitivity and change in glucose tolerance. As this relationship is shown by a straight line inclined at 45° then it can be deduced that equal changes in insulin sensitivity are associated with equal changes in glucose tolerance. This deduction, if correct, means that if the sugar tolerance areas corresponding to several diets and the insulin depression areas for two of these diets are known in one individual, then the insulin depression areas corresponding to each one of the series of diets may be calculated. The requisite data and the results of this calculation are given in Table VIII, and it will be seen that the calculated insulin depression areas agree closely with the actual areas determined experimentally. In view of this agreement between the calculated and the observed results it may be concluded that the correlation between change in insulin sensitivity and change in sugar tolerance is accurately expressed by a straight line inclined at an angle of 45° .

This correlation permits important deductions to be made with regard to the nature of the glucose tolerance curve.

Zuntz and la Barre (14) have shown that a rise of blood sugar is an adequate stimulus to the secretion of pancreatic insulin. In each sugar tolerance test, therefore, the hyperglycæmia, following oral glucose, will evoke a secretion of pancreatic insulin which will manifest its action by restricting the rise of blood sugar to the limits revealed by the blood sugar curve. At first sight this work would appear to offer an easy explanation of the improving tolerance consequent upon increase of dietary carbohydrate, for it could be postulated that the secretion of endogenous insulin is progressively facilitated by diets containing increasing amounts of carbohydrate so that the hyperglycæmia following glucose ingestion is proportionately restricted. But it is obvious from a consideration of Fig. 9 that the increasing sensitivity of the individual to insulin must play a considerable part in this progressive restriction of hyperglycæmia after oral glucose, and a little further consideration will show that the improvement in sugar tolerance consequent upon increase in the amount of carbohydrate in the diet is completely explained by the coincident increase in insulin sensitivity.

TABLE VIII

Table giving the data necessary to calculate the insulin depression areas on the basis of the relationship demonstrated in Fig 10 The two right-hand columns show the calculated and the observed results

Subject	Sugar tolerance		Insulin depression area		Calculated insulin depression area	Measured insulin depression area
	Area	Difference from 1	Measured	Difference from 1		
C	1 10,890		1 366			
	2 10,750	140	380	14		
	3 9,100	1,790	552	186	545	552
M	1 13,690		1 405			
	2 11,960	1,730	460	55		
	3 5,490	8,200	675	270	666	675
	4 5,400	8,290	710	305	670	710
I	1 6,837		1 30			
	2 3,785	3,048	(54*)		97	(54*)
	3 3,560	3,273	97	67	103	97
	4 2,850	3,983	119	89	(119)	(119)†
	5 2,767	4,066	130	100	121	130
	6 1,815	5,018	152	122	142	152
	7 1,136	5,697	154	124	157	154

* This insulin depression curve was unsatisfactory See the note at the end of section on results

† The glucose tolerance and insulin depression areas of experiments 4 were used as the basis of calculation for this subject

Let us consider what would happen to the glucose tolerance area if the amount of endogenous insulin brought into action as a result of the glucose tolerance test actually did increase as the subject received diets containing larger and larger amounts of carbohydrate In this event with each increase of dietary carbohydrate two factors would be brought into play to reduce the tolerance area, an increase in the amount of effective insulin and an increase in the sensitivity to this insulin It has been shown by actual measurement that the change in insulin sensitivity for each increase of dietary carbohydrate is exactly the same as the change in glucose tolerance (Fig 10) Now if the quantity of effective insulin is also increased the restriction of the

hyperglycæmia after glucose will be disproportionately greater than the increase in insulin sensitivity, so that the tolerance area will be disproportionately reduced and the equation change in insulin sensitivity = change in glucose tolerance will not exist. But this equation is established by experiment. Therefore, the effective endogenous insulin cannot be increased as a result of increasing the amount of carbohydrate in the diet. And by similar consideration it can be shown that the quantity of effective insulin cannot be decreased in response to these dietary changes. The only condition of endogenous insulin supply that is compatible with the demonstrated relationship between change in glucose tolerance and change in insulin sensitivity (Fig 10) is that in healthy individuals the effective endogenous insulin is uninfluenced by changes in dietary carbohydrate and that the amount brought into action is the same in each glucose tolerance curve whatever the degree of tolerance indicated. The only factor which varies in proportion to change in glucose tolerance is change in insulin sensitivity and therefore the sugar tolerance must be determined by the sensitivity of the individual to his endogenous insulin, for the linear relationship demonstrated in Fig 10 shows conclusively that there can be no other factor affecting glucose tolerance but insulin sensitivity.

In the light of these observations the glucose tolerance curve acquires a new significance for now it can be regarded as the expression of the healthy individual's sensitivity to his endogenous insulin.

It may therefore be concluded that in healthy subjects the increasing glucose tolerance, consequent upon increasing amounts of dietary carbohydrate, is completely accounted for by the increase in insulin sensitivity induced by these changes in diet.

Application of the results

It has been shown that the determination curve of insulin sensitivity is of the same shape as the determination curve of glucose tolerance (Fig 8). It will be seen that as the utilization of carbohydrate falls the sensitivity to insulin diminishes also. Let us consider the train of events in a case of pancreatic diabetes mellitus. As the insulin supply is slowly restricted by disease the utilization of carbohydrate will diminish, a corresponding diminution in insulin sensitivity will ensue and a vicious cycle will set in—the more the insulin supply is reduced the more the sensitivity diminishes. Finally when the utilization of carbohydrate falls below that corresponding to 50 g of dietary carbohydrate daily the sensitivity will diminish so rapidly that diabetes mellitus will suddenly appear, although the restriction of insulin may be proceeding at the same slow rate (Fig 8). If now such a patient is balanced with insulin on a diet containing 50 g or 60 g of carbohydrate he will not be producing the maximum insulin sensitivity of which he is capable. Increase of the carbohydrate content of the diet to 150 g or 200 g of carbohydrate

will enable a great increase in sensitivity to be produced (Fig 8) with the result that this increase in dietary carbohydrate will not require a proportionate increase in insulin to ensure its utilisation by the body. These considerations provide a logical explanation of a clinical paradox which has recently attracted much attention. It is found that if diabetics are balanced with insulin on a low carbohydrate diet, e.g., 50 g daily, then trebling or quadrupling the daily intake of carbohydrate rarely necessitates any increase of insulin dosage, that if increase of dosage is necessary it is extremely small, and that in some cases reduction of the daily amount of insulin can be effected. It will be seen from the insulin sensitivity determination curve (cf Fig 8) that as the dietary carbohydrate is increased from 50 g to 200 g marked increase in insulin sensitivity, and consequently of the ability of the body to dispose of carbohydrate occurs, with increase from 200 g to 350 g little increase in sensitivity results and the sugar tolerance improves but slightly, and with increase from 350 g to 450 g a further but less marked improvement appears. It appears therefore that in the case of the diabetic balanced with insulin, increase in the carbohydrate content of the diet from 50 g to 200 g will necessitate little or no increase in insulin dosage, that increase of dietary carbohydrate from 200 g to 350 g will produce such little improvement in insulin sensitivity that proportionate increase of the dose of insulin will be required, and that further increase of the daily amount of carbohydrate from 350 g to 450 g will cause a second increase of insulin sensitivity which will necessitate the insulin requirements being increased but slightly. This suggests that the maximum disposal of dietary carbohydrate by each unit of insulin will be obtained when a diet containing 200 g of carbohydrate is given. For amounts both above and below this figure more insulin will be required for each gram of dietary carbohydrate.

The experiments given in this paper also provide an explanation of the work of Allan (3) on the glucose equivalent of insulin in depancreatized dogs. He showed that in such animals the greater the amount of carbohydrate given the smaller the amount of insulin required to ensure the retention of each gram of carbohydrate in the body. In the light of my experiments it is probable that Allan's result was due to the increasing amounts of dietary carbohydrate producing increasing sensitivity to insulin.

The work of Adlersburg and Porges (2) and of Sweeney (12) was mentioned at the beginning of this paper and it was noted that they had each suggested that the beneficial effect of a high-carbohydrate low-fat diet on sugar tolerance might be due to the same mechanism as that which brings about improving sugar tolerance with consecutive doses of glucose (Staub-Traugott effect). In a previous communication (9) I have shown that the Staub-Traugott effect is produced by the organism's increasing sensitivity to insulin consequent upon the repeated

doses of glucose In this paper it has been shown that the beneficial effect of a high-carbohydrate low-fat diet is due to the increased sensitivity to insulin which is brought about solely as the result of the large amount of carbohydrate in the diet The suggestion of the above workers is, therefore, justified and the identity of the mechanism underlying both the beneficial effect on tolerance of high-carbohydrate diets and also the Staub-Traugott phenomenon, is definitely established

The results presented in this paper demonstrate that the efficiency with which insulin acts in a particular individual is determined by the sensitivity of that individual to insulin It is, therefore, permissible to suggest that a type of diabetes mellitus may exist which is not due to diminution of the secretion of pancreatic insulin, but is due to impairment of the individual's sensitivity to the insulin secreted In such a case, although the output of pancreatic insulin may be normal in quantity, the diminution in amount of the factor productive of insulin sensitivity would produce a result identical with that of impaired production of insulin—namely the clinical picture of diabetes mellitus Clinical evidence in favour of this suggestion has been summarised elsewhere (10)

The nature of the factor which determines insulin sensitivity is still unknown, but in previous publications (7) (8) I have suggested on the basis of indirect evidence that the factor is an activator of insulin and that its production is stimulated by the ingestion of carbohydrate

SUMMARY AND CONCLUSIONS

1 Experiments are described on healthy human subjects concerning the effect of change in composition of the diet on the glucose tolerance and the sensitivity to insulin

2 It is shown that the area demarcated by the glucose tolerance curve above the resting blood sugar level, and similarly the area demarcated by the insulin depression curve below the resting blood sugar level remains constant for the same individual if the composition of the diet is maintained unchanged

3 Experiments are described which demonstrate that in healthy subjects the improvement in glucose tolerance, consequent upon the change from a low-carbohydrate high-fat diet to a high-carbohydrate low-fat diet, is determined neither by change in the calory value nor ketogenic-antiketogenic ratio nor change in the fat nor protein content of the diet, but solely by the amount of carbohydrate in the diet On the basis of these experiments a "Determination curve of glucose tolerance" has been constructed which expresses for healthy subjects the relationship between the change in sugar tolerance and the change in amount of dietary carbohydrate

4 It is demonstrated that the efficiency with which a standard dose of crystalline insulin acts on the blood sugar is determined by the carbohydrate content of the diet so that the greater the amount of carbohydrate in the diet the greater the sensitivity of the organism to insulin. The relationship in healthy subjects between change in insulin sensitivity and change in the amount of carbohydrate in the diet can be expressed as a "determination curve of insulin sensitivity"

5 A correlation between change in glucose tolerance and change in insulin sensitivity has been demonstrated which is such that it can be expressed as a straight line inclined at an angle of 45° to the abscissa

6 On the basis of these results it is concluded that —

- (a) The development of insulin sensitivity is independent of the dose of insulin used as the standard test dose
- (b) The quantity of pancreatic insulin brought into action in response to a standard dose of glucose is constant in amount whatever the degree of tolerance indicated by the blood sugar curve
- (c) The change in glucose tolerance consequent upon change in composition of the diet from a low-carbohydrate high-fat to a high-carbohydrate low-fat diet is completely accounted for by the change in sensitivity of the individual to the insulin secreted by his own pancreas

7 The bearing of these results on the apparently acute development of diabetes mellitus in man and on the dietetic therapeutics of this disease is discussed

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THE DIET OF DIABETICS PRIOR TO THE ONSET OF THE DISEASE

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It is now securely established that the glucose tolerance of a healthy individual is determined by the composition of the diet which he is receiving. In 1926 Adlersberg and Porges (1) and in the following year Sweeney (11) clarified and extended the fragmentary observations of earlier workers by clear demonstrations that the sugar tolerance of healthy individuals was impaired by administering a low-carbohydrate high-fat diet, whilst it was improved when a high-carbohydrate low-fat diet was taken. More recently it was shown by one of us (H P H, 8) that the sole dietetic factor determining this variation in tolerance is the absolute amount of carbohydrate in the diet and further it was demonstrated that, for healthy subjects in general, a definite and mathematically constant relationship exists between the carbohydrate content of a diet and the degree of tolerance produced by this particular diet. In previous papers (5) (6) (7) the effect of change in composition of the diet on the efficiency with which a standard dose of insulin acted on the blood sugar had been investigated and the general conclusion had been reached that those diets which cause improvement in sugar tolerance also cause increase in the sensitivity of the organism to insulin, whilst those diets which produce impairment in sugar tolerance produce a decrease in insulin sensitivity. In the paper previously referred to (H P H, 8) these generalisations were placed on a precise basis and it was shown that the dietetic factor determining insulin sensitivity was the carbohydrate content of the diet, that change in amount of dietary carbohydrate produced exactly equal change in sugar tolerance and sensitivity to insulin, and that the change in glucose tolerance, consequent upon change in the amount of carbohydrate in the diet, was completely accounted for by the change in sensitivity of the individual to the insulin secreted by his own pancreas.

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Having established the existence of a factor whose presence in the body is necessary to render the individual sensitive to insulin, it was realised that restriction of this factor would produce a result indistinguishable from that of restriction of the supply of pancreatic insulin, that is grossly impaired sugar tolerance and the clinical picture of diabetes mellitus. And it having further been shown that the amount of this sensitising factor in the tissues of normal individuals is determined by the composition of the diet received, it occurred to us that ingestion of a diet, which did not elicit production of the full amount of insulin sensitivity, might in the course of time result in permanent impairment of insulin sensitivity with the consequent appearance of diabetes mellitus. The problem, therefore, that we set ourselves to investigate was this, do diabetics, prior to the onset of the disease, take diets relatively low in carbohydrate and relatively high in fat such as have been shown to produce in normal subjects impairment of insulin sensitivity and of carbohydrate tolerance?

For the purpose of this investigation two groups of human subjects were used, namely, a group of diabetic patients and a control group of non-diabetic subjects, all these subjects were socially of the "hospital class" and attending University College Hospital.

The diabetic group

The diabetic group contained 143 cases of proved diabetes mellitus. In the majority of these cases the diagnosis could be made on the history and routine examination alone, but in the minority, in which these means did not provide sufficiently definite information, the diagnosis was established by the result of a sugar tolerance test. At the commencement of the investigation 50 cases were taken from the diabetics already attending hospital, but these patients had all come under treatment sufficiently recently for them to remember their proclivities as regards diet when their preferences were unfettered. The remainder of the cases formed a continuous sequence of new cases attending the Diabetic Clinic at University College Hospital during the last 18 months. All these new patients were submitted to investigation regarding their diet prior to the onset of the disease, as soon as the diagnosis was made and before any instructions were given them as regards dietetic treatment. As the majority had received, from their private doctors, nothing but the vaguest instructions regarding the dietetic treatment of their disease and as only a short time had elapsed since these instructions were given, a knowledge of therapeutic dietetic restrictions played little or no part in determining the dietetic preferences of these patients.

As it was desired to classify the diabetics according to the age at which the diabetes appeared, an attempt was made, by enquiring into each patient's history, to date the onset of the disease. In the young patients in whom the disease has a relatively rapid and severe onset this time could usually be fixed definitely to within a month or two of

some well remembered date, but in the older patients, in whom the disease appears more insidiously, the probable time of its appearance could not be localised as a rule more accurately than within a season of some particular year. In a few old diabetics even this accuracy could not be attained and we were forced to take the time at which glycosuria was discovered as the time of onset of the disease.

The findings to which we came to attach most weight as indicating the time of appearance of the disease were glycosuria, nocturnal frequency of micturition and in women vulvitis. In the rare cases in which glycosuria had been fortuitously detected before the symptoms of diabetes forced the patient to seek medical advice, the appearance of the disease was dated from the time of this finding. A history of nocturnal frequency of micturition appearing some time previously and persisting in varying degree until the time of examination, was, in the absence of any other cause of frequency, taken as presumptive evidence of the time of onset, and naturally the more sudden the appearance and the more marked the frequency the more probable did this presumption become. Vulvitis in women, though by no means a constant symptom, was found to be of considerable value for our purpose, but it was realised that this symptom did not develop until some little time after the onset of glycosuria. The vulval irritation usually varies in intensity after the time of its appearance, but it is always intense during exacerbation of the disease and hence is usually present when the patient comes for medical advice. For this reason the patient, when questioned, is in no doubt as to the nature of the symptom and owing to its distressing nature she has little difficulty in recollecting the time of its first appearance. Thirst, disturbances of vision consequent on changes in refraction, asthenia and loss of weight were each encountered in many patients and, when present, they offered valuable confirmatory evidence. These symptoms, however, tend to be most marked in those patients in whom the disease appears so abruptly that there is little doubt as to the time of onset, and, in cases with insidious onset, are less frequently present than the finding of glycosuria, nocturnal frequency of micturition, or vulval irritation. It should be noted, that even in cases in which the disease appears insidiously it is unusual not to elicit the time of onset of at least two symptoms to help one in localising the appearance of the diabetes.

The approximate age at the onset of the disease having been decided, the patients were classified in groups. Fig 1 shows for our series the number of diabetics of either sex developing the disease at the different ages. These age incidence curves are very similar to the curves given by Joslin, Dublin and Marks (3), showing the American mortality from diabetes mellitus at different ages. If it is allowed that the national mortality from diabetes reflects the incidence of the disease then it will be conceded that in our 143 diabetics the age incidence is the same as in diabetics in general. In another paper (4) the above workers have

shown that obesity and diabetes are closely associated. Our present series of diabetics yield evidence in support of this finding, for 60.1% were overweight on first coming up for treatment. It may, therefore, be concluded that our series of diabetics is a representative sample of the general diabetic population of the country.

In one respect the range of ages of onset in the diabetic group was artificially curtailed. Cases under 16 years and over 75 years were excluded as it was feared their replies to questions might be unreliable, and one or two cases under 75 years were excluded on the ground of premature senility rendering their statements untrustworthy.

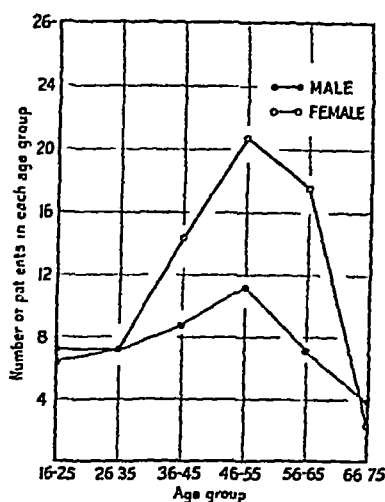


Fig 1 Figure showing number of patients in our series of cases, developing diabetes mellitus at different ages

It is a well-established clinical observation that cases of diabetes mellitus fall into two groups, the young diabetics developing the disease before 45 years of age, in whom the disease tends to have a sudden onset, to be unassociated with arterio-sclerosis and to be, in general, of a severe type, and the older diabetics, developing the disease after 45 years of age, in whom the disease is of insidious onset, associated with arterio-sclerosis and tends to run a mild course. The disease in these two groups is so different as to suggest that we are dealing with two distinct types of diabetes mellitus. For this reason the diabetic and control subjects were each divided into two sections, one containing those subjects under 45 years and the other those over 45 years. These sections were further separated into male and female groups. The results obtained by the quantitative method both for diabetic and normal subjects were thus classified into four sections—males 16-45 years, females 16-45 years, males 46-75 years, females 46-75 years.

The normal group

Two control groups of non-diabetic subjects were used. One containing 131 subjects served as the control group for the "qualitative" method, the other containing 137 subjects as the control for the "quantitative" method.

These subjects were taken mainly from in-patients of University College Hospital. Subjects suffering from any complaint which interfered with appetite or digestion, were excluded. The majority of the cases were surgical, obstetrical or gynaecological, but a considerable number of patients convalescent from infections, suffering from chronic arthritis, hypertension, arterio-sclerosis, and cardiac cases without failure, were included.

The age distribution in this group was determined by the age incidence distribution in the diabetic group, and an attempt was made to obtain as many non-diabetics in any particular age group as there were diabetics whose disease commenced at this age. Although this object was not completely realised, yet it will be seen from Table II that the age distribution of the diabetic and non-diabetic groups was sufficiently close to justify our regarding them as comparable series. Apart from the selection consequent on this necessity of ensuring a similar age distribution in the two groups the normal subjects were entirely unselected. A certain number of control subjects of a particular age was required and these were obtained by taking consecutive subjects of that age as they were encountered in the wards.

Methods of investigating the diet

Two different methods were used to ascertain the composition of the diet habitually chosen by the individual subjects of the normal group and by those of the diabetic group before the onset of the disease. For convenience of discussion one method may be termed the "qualitative" method and the other the "quantitative" method, the first aimed at detecting qualitative variations in composition of the diet, the second at assessing quantitative variations in the intake of ordinary foodstuffs. The former method was used exclusively by one investigator (H. P. H.) and the latter by the other (E. M. M.).

Both methods of investigation were used on each of the diabetic patients but the results, on each patient, obtained by the two methods were not compared until the completion of the investigation. Thus the investigator using the qualitative method was uninfluenced by the results obtained by the investigator using the quantitative method. In the two normal control groups different patients were seen by each investigator.

A preliminary enquiry was made to ascertain whether any change in dietary habits had been noticed by any diabetic patient after the symptoms of his disease appeared. From some subjects this elicited the

answer that since the symptoms appeared a strong partiality for sweet foods had been noticed to develop. One diabetic, for example, stated that from a distaste of sweet things he had begun to eat 3 lbs of jam a week. Such alterations were remarked only in those diabetics in whom the onset of the disease was sudden, but this information did leave a suspicion in our mind that in cases in which the disease had an insidious onset a similar insidious change of taste may have occurred, in which case our figures for the diets of such patients will indicate the consumption of too high a proportion of carbohydrate.

The "qualitative" method The object of this method was to elicit information regarding abnormalities of individual taste and of preference for different foodstuffs.

In order to make use of this method it was necessary first that the investigator should be conversant with variations in normal taste and preference. To this end 131 normal subjects of appropriate ages were questioned, their replies noted down and an attempt thus made to arrive at a conception of the type of diet eaten by the majority of persons in this social class. The same questions were then put to the diabetic patients, and finally the two groups compared.

The subject was first asked whether his relatives and friends had remarked any particular preference in his selection of food. It was ascertained whether he was considered a "sweet tooth," or a large "meat eater," or a person with a preference for fat, or whether his dietary habits were such as to excite no special comment. He was next interrogated as to his preference for different foodstuffs. It was early discovered to be impossible by means of this method to elicit definite information as to the consumption of foodstuffs which had no definite characteristic quality. The questions, therefore, soon came to be confined to those concerning strongly characterised foodstuffs which allowed definite expression of individual taste.

Of the carbohydrate foodstuffs the most definite information was forthcoming with regard to sweet substances. The subjects were asked whether or not they had a liking for jams or marmalade and an attempt was made to get a rough idea of the frequency and quantity in which these substances were eaten. Consumption of sugar by itself was a rare abnormality, but significant information was often obtained when the subject was asked how much sugar was taken in tea and whether he was in the habit of sweetening still further dishes such as milk puddings, stewed fruit, tarts, etc., when these dishes were brought to the table sweetened to a degree which was acceptable to the rest of the family. Information with regard to the taste for bread was unsatisfactory as so many of the men took sandwiches for mid-day lunch. But some information was forthcoming about potatoes. When the subjects were asked how many new potatoes the size of a hen's egg they would consume at a meal, considerable variations in taste were elicited.

We were unable to frame any useful questions which would reveal a preference for protein foodstuffs. But one question in relation to meat consumption proved to be extremely valuable. That was, "What kind of meat do you like—fat or lean?" In reply definite statements of preference or indifference were the rule. Most people seem to have a clear idea of their tastes in this direction, and we think that a division of persons according to their replies to this question alone would not be devoid of significance.

The individual preferences regarding fatty foodstuffs were more easy to estimate than those concerning carbohydrate. This is probable because fatty foods are not eaten casually between meals, as carbohydrates often are, but are taken in conjunction with other food and in definite amounts which the individual knows to be to his taste. Liking for butter can be estimated by the patient's statements as to the thickness with which it is spread on bread, and not uncommonly such abnormalities as the spreading of more butter on bread already buttered will be encountered. Liking for dripping is often easy of detection, for, most of our patients coming from families who rarely have a joint more than once a week, the satisfying of such a preference may result in the patient's habits being brought to his notice by the other members of the household. Cream, as a rule, was only accessible to those of our patients who lived in the country but when it was available definite likes and dislikes were usually stated. For this substance town patients not infrequently showed a distinct partiality, by admitting their failing for surreptitiously skimming the cream from the household milk supply, but, naturally, we could not offset such information by a knowledge of how many town patients would dislike cream if it were more easily available. The other fatty foods are not usually taken in a pure form and as the amount of these included in any particular dish depends upon the taste of the cook concerned, patients were not questioned on these points.

After questioning a number of normal subjects in the above manner one acquires a general idea as to the normal standards of taste, and thereafter, considerable departures from this normal standard obtrude themselves on one's notice. For this reason we have ventured to classify our patients—diabetics and normal controls—on this rough basis. Immediately after the interrogation of a patient his preference for either carbohydrate or fat were classified either as normal, increased or greatly increased. This being done, the subjects could be divided into two groups, those whose tastes inclined to a fatty diet, and those whose tastes inclined to sweet foods. It was not often that difficulty was experienced in deciding whether the same patient's dietary preferences were normal or whether he showed an increased liking for fatty or for carbohydrate foods.

It should be noted that this method elicits information regarding the proportion of salient foodstuffs in the diet in relation to the other components and that it throws no light on the amounts of the different foods ingested.

The great limitations of this method being recognised we still think that it provides results which in a general sense are of significance

The "quantitative" method The object of this method was to give quantitative expression to the patient's choice of food. It should be noted that the method takes into account only the subject's preference for the common varieties of foodstuffs, and those perversions of taste which are occasionally discovered in diabetics, lie outside its scope

The subject to be investigated was shown different amounts of various commonly used foods. Slices of bread of varying size and thickness, jam, pats of butter of different weight, samples of lean and of fat meat, potatoes, fruit, and average helpings of various popular puddings were displayed, and in addition simple household measures were to hand to aid his choice of the amount of food. The subject was asked to choose, from the foodstuffs before him, a breakfast, a mid-day meal, a tea, and a supper, similar to those of his daily dietary when he was allowed free choice, and the amounts and nature of the foods chosen were noted down. Enquiry was then made as to foods habitually eaten which were not included in those displayed, the amount of such foods consumed was assessed by the subject in terms of household measures, and included in the list of the diet. The approximate composition of all the foodstuffs chosen being known from tables of food analyses, the daily (10) diet could now be expressed in terms of carbohydrate, protein and fat

At first sight it would be expected that the figures obtained by this method would vary considerably in duplicate estimations, but it is surprising how constant the results in any one patient remain. The individual items of food in the meals may vary but the total amounts of carbohydrate, of protein and of fat chosen for the daily intake remain remarkably constant. For example, one patient at the first interrogation chose a diet containing 219 g of carbohydrate, 45 g of protein, 58 g of fat, and at the second questioning four months later her diet worked out at 213 g of carbohydrate, 56 g of protein and 50 g of fat. And a second new diabetic patient, who was re-questioned the next day because her diet appeared to be so abnormal, chose a second diet which did not differ more than a few grams from her first diet of carbohydrate 156 g, protein 35 g, and fat 158 g. It would appear then that the results of this test may be taken as yielding significant information with regard to the composition of the diet habitually preferred by the subject

When the investigation of the diabetic and control series by this method was completed the results were submitted to statistical analysis, and we are greatly indebted to Professor Major Greenwood for performing this operation

Results obtained by the "qualitative" method

In Table I are shown the results obtained by the qualitative method of investigation. It will be seen that the percentage of diabetics who expressed a preference for diets containing an excessive proportion of fatty foods is $2\frac{1}{2}$ times as great as the percentage of control subjects with the same preference. Similarly the proportion of subjects in the

TABLE I

Table giving the results obtained by the "qualitative" method of investigation and showing that diabetics as a whole tend to take diets containing an excessive proportion of fatty foodstuffs

Group of	Percentage of subjects taking —			
	Excess of fat in diet	Excess of butter dripping, cream	Preferring fat to lean meat	Excess of carbohydrate
131 Diabetics	76.3	70.2	46.0	20.0
118 Normals	34.0	30.0	16.0	34.0

diabetic group who expressed a decided partiality for butter, dripping and cream is $2\frac{1}{2}$ times as great as in the control group, and the percentage of diabetic subjects who definitely preferred fat to lean meat or meat containing the usual amount of fat, was 3 times as great as the percentage of normal subjects who evinced the same partiality. On the other hand, the percentage of diabetics with a partiality for sweet foods was less than $\frac{2}{3}$ of the percentage of normal subjects with same trait.

Gross aberrations of dietary choice are not capable of expression in figures but some indication may be given of the type of abnormality that is not infrequently encountered in individual diabetics.

One diabetic in the early twenties informed us that when a child he was constantly incurring parental correction for his habit of cutting fat off uncooked meat, or appropriating lumps of suet and eating these substances raw. Another diabetic, aged 26, before the onset of her disease, removed the fat from the uncooked joint, roasted it separately and then ate it as her own particular delicacy. A considerable number of patients confessed to their weakness for eating butter in spoonfuls, without consuming bread at the same time. Many patients had apparently established their right to the fatty portions of the meat, and two heads of families reported that they always cut all the fat from the cooked meat and ate it without or with only a little lean.

No excesses with regard to sweet foods were discovered in the diabetics but 14 of the 131 normal subjects revealed a marked preference for jams and marmalade. None of the control subjects showed a partiality for fatty foods which was comparable in any way with the abnormalities of taste recorded above in the diabetics.

Results obtained by the "quantitative" method

Table II shows the results obtained by the quantitative method for each of the four groups into which diabetic and control subjects were divided according to age and sex

Reference to the age column will show that the series of diabetic and normal subjects constituting each of the four groups were comparable

TABLE
Table showing the diets chosen by normal subjects and by diabetics, prior

	Number of Subjects	Age		Daily calories	Carb	
		Mean	S.D.		Mean	S.D.
<i>Males, 16-45</i>						
Diabetics	29	30.4 ± 1.7	8.98	3759	482 ± 21	113.8
Normals	32	32.5 ± 1.4	7.82	3116	441 ± 20	111.9
Diff. Diabetics—normals		— 2.12 ± 2.17			40.69 ± 28.96	
Diff./S.E.		— 0.98			1.41	
<i>Males, 46-75</i>						
Diabetics	28	56.6 ± 1.4	7.31	3247	397 ± 20	104.6
Normals	28	54.8 ± 1.3	6.83	2704	384 ± 24	125.6
Diff. Diabetics—normals		1.82 ± 1.89			13.86 ± 30.89	
Diff./S.E.		0.96			0.45	
<i>Females 16-45</i>						
Diabetics	35	33.9 ± 1.4	8.31	2837	365 ± 17	101.9
Normals	36	32.9 ± 1.3	7.99	2436	343 ± 17	104.0
Diff. Diabetics—normals		1.02 ± 1.93			22.40 ± 24.4	
Diff./S.E.		0.53			0.92	
<i>Females, 46-75</i>						
Diabetics	51	55.7 ± 0.80	5.71	2522	324 ± 14	100.4
Normals	41	55.1 ± 1.0	6.56	1861	254 ± 9.3	59.8
Diff. Diabetics—normals		0.65 ± 1.30			70.6 ± 16.87	
Diff./S.E.		0.50			4.18	
All Diabetics	143			2997		
All Normals	137			2478		

S.D. = standard deviation

We are indebted to Professor Major Greenwood for

from the point of view of age distribution. Slight differences do exist between the average ages of each group but these differences are slight and are such as to be unavoidable when comparing any two groups of human subjects one of which has accumulated by chance (the diabetics) and one of which (the normals) has been selected to be as near comparable as possible to the other in some particular respect.

II

to the onset of their disease, as determined by the quantitative method

Diet		Percentage calories from							
Prot		Fat		Carb		Prot		Fat	
Mean	S D	Mean	S D	Mean	S D	Mean	S D	Mean	S D
109 ± 5.3	28.61	155 ± 6.5	34.88	51.3 ± 0.82	4.42	11.6 ± 0.35	1.89	37.1 ± 0.77	4.15
95 ± 4.2	23.97	108 ± 5.1	28.69	56.6 ± 0.83	4.69	12.3 ± 0.37	2.09	31.1 ± 0.77	4.31
14.53 ± 6.80		46.74 ± 8.23		-5.37 ± 1.17		-0.66 ± 0.51		6.02 ± 1.09	
2.14		5.68		-4.59		-1.29		5.52	
104 ± 6.2	32.89	138 ± 9.6	50.72	49.2 ± 1.2	6.11	12.8 ± 0.46	2.42	38.0 ± 1.1	5.84
88 ± 5.1	27.19	98 ± 8.5	44.72	57.3 ± 1.0	5.33	12.6 ± 0.50	2.67	30.1 ± 0.86	4.53
20.21 ± 8.07		45.18 ± 12.78		-8.10 ± 1.53		0.19 ± 0.68		7.90 ± 1.40	
2.50		3.54		-5.29		0.28		5.64	
81 ± 3.1	18.57	117 ± 5.9	34.87	51.3 ± 1.2	7.11	11.8 ± 0.41	2.42	37.0 ± 1.1	6.20
69 ± 2.7	16.03	87 ± 3.7	21.95	55.7 ± 1.0	5.69	11.7 ± 0.44	2.63	32.6 ± 0.83	4.99
11.64 ± 4.12		29.42 ± 6.93		-4.44 ± 1.53		0.07 ± 0.60		4.37 ± 1.34	
2.83		4.25		-2.90		0.12		3.26	
76 ± 2.6	18.56	102 ± 5.0	35.63	51.3 ± 1.0	7.40	12.3 ± 0.36	2.54	36.5 ± 1.1	7.79
59 ± 2.1	13.12	68 ± 2.5	16.06	54.3 ± 1.0	6.20	12.9 ± 0.46	2.93	32.3 ± 0.80	5.09
16.58 ± 3.31		34.7 ± 5.59		-3.03 ± 1.42		-0.66 ± 0.58		3.68 ± 1.35	
5.01		6.21		-2.13		-1.14		2.73	
				50.9		12.1		37.0	
				55.9		12.3		31.8	

S E = standard error
performing the mathematical analysis shown in this table

The next column gives the calory intake of food in each of the groups. It will be seen that the males take more food than the females, that the daily consumption of food falls with increasing age, and that diabetics chose diets which are of a considerably higher value than do normal subjects in the comparable groups.

The next section of the table is divided into three columns. In the first is given the absolute amount of carbohydrate, in the second the absolute amount of protein and in the third the absolute amount of fat. The figure for each group represents the mean value of the amount of this foodstuff chosen by the subjects of that group for their daily diet. Here again it can be seen for each foodstuff that males take more than females, that the consumption falls with increasing age, that diabetics chose larger amounts than do the corresponding control subjects.

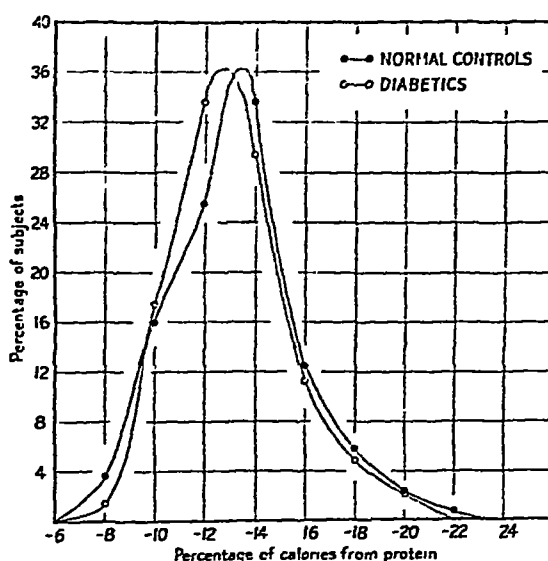


Fig 2 Curves showing for the diabetic and normal groups of subjects the percentage of subjects in each group choosing diets yielding the various percentages of calories from protein

The last section of Table II gives the percentage calories derived from each of the three main foodstuffs. In the first column of the section are shown the percentage of calories derived from carbohydrate. It will be seen that in each of the four groups diabetics derive a smaller proportion of their calories from carbohydrate than do the corresponding normal subjects. In only one group, females 46-75, does the ratio difference between diabetics and normals fall materially below 3, and standard error

it may, therefore, be concluded that, from a mathematical point of view, the diminished proportion of calories derived from carbohydrate found in the freely chosen diet of the diabetic is definitely outside the limits

of chance error In the next column are set out the percentage calories derived from protein In all four groups the difference between the figures for diabetics and normal controls is small and in all cases the ratio difference between diabetic and normals $\frac{\text{difference between diabetic and normals}}{\text{standard error}}$ is far below 3 The percentage of calories derived from protein is, therefore, for practical purposes the

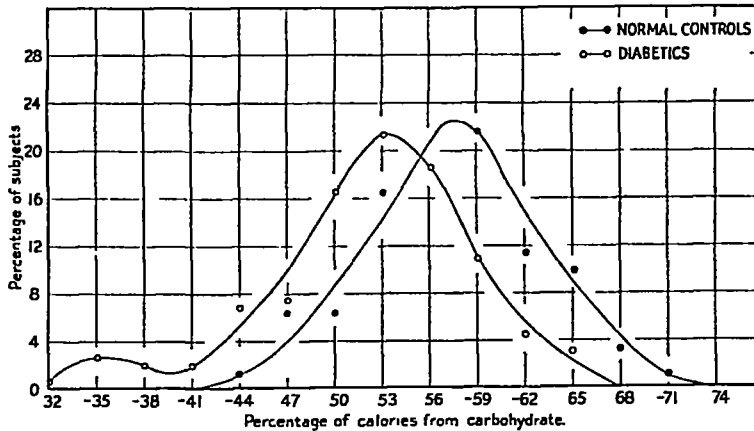


Fig 3 Curves showing the percentage of diabetic subjects and the percentage of normal subjects choosing diets yielding particular percentages of calories from carbohydrate

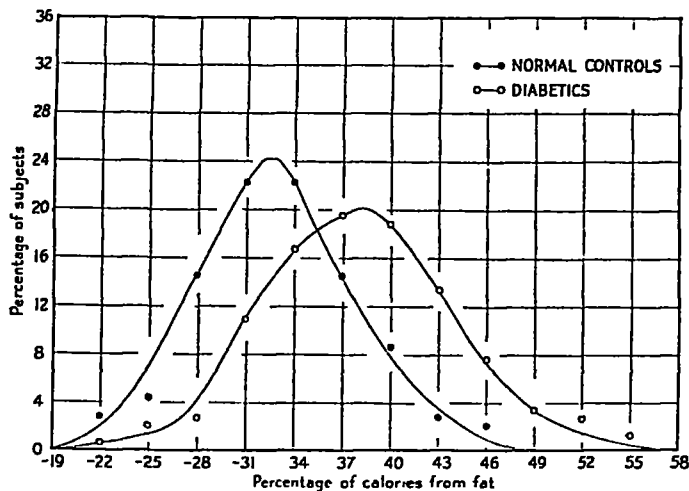


Fig 4 Curves showing the percentage of diabetic subjects and the percentage of normal subjects choosing diets yielding various percentages of calories from fat

same in both diabetics and normals The last column shows the percentage of calories derived from fat In all four groups the diabetics will seem to take a greater proportion of calories as fat and the fact that the ratio

difference between diabetics and normals
standard error is in all, save the group of females age 46-75, greater than 3 and in this group almost 3, shows that this difference is well outside the limits of error in sampling

This last series of figures, therefore, shows that diabetics, in comparison with normal subjects, choose diets yielding a smaller proportion of calories from carbohydrate, a greater proportion from fat and the same proportion from protein. The general averages for all diabetics and all normals are shown in the bottom two lines of Table II

In Figs 2, 3 and 4 the results are depicted in another way. In the case of carbohydrate, of protein and of fat, the diabetic and the normal subject have each been sorted into classes according to the percentage of calories they derive from these three sources. The number of individuals in each class has then been expressed as a percentage of the total number of diabetics or control subjects. For example, diets deriving 47% to 50% of their calory value from carbohydrate were chosen by 24 out of 143 diabetics, i.e., 16.8%, whilst similar diets were chosen by 9 out of 137 normal control subjects, i.e., 6.6%. Figs 2, 3 and 4 were constructed by charting the percentage of calories derived from the particular foodstuff against the percentage of diabetic or control subjects choosing a diet of that composition. The curve thus obtained expresses the frequency with which any particular type of diet was chosen.

In Fig 2 the curves for the percentage of calories derived from protein are given. It will be seen that there is no material difference between the curve for diabetics or the curve for normals. Both groups have the same range of dietary choice.

Fig 3 shows the distribution of the choice of calories from carbohydrate in the diabetic and control groups. The mode of the diabetic curve is 53% of calories from carbohydrate, the mode of the normal control group 58% of calories from the same source. The majority of diabetics, therefore, prior to the onset of their disease tend to choose diets yielding a smaller proportion of calories from carbohydrate than do a corresponding group of normal subjects.

Fig 4 gives the curves for percentage of calories derived from fat. The mode of the diabetic distribution curve is 38.5%, for the control distribution curve 32.5%. Diabetics, therefore, prefer diets in which a larger proportion of the calories than normal are derived from fat.

DISCUSSION

The accuracy of the results

Before discussing the significance which may be attached to the data obtained in this investigation it is necessary to consider the various sources of inaccuracy inherent in the methods used and to assess the extent to which these inaccuracies may invalidate the apparent significance of the figures obtained.

One possible error, which will doubtless suggest itself to the reader, is that the investigators may have suggested the difference in diets to the two groups of patients by unconsciously phrasing their questions differently to each group. This suggestion would hardly explain the gross aberrations of taste which were detected, but perhaps the strongest argument against this suggestion is that the results surprised us in two ways. Firstly, from our hypothesis we had expected to find that if diet played any part in determining the appearance of the disease then it must needs operate for years and consequently only the older diabetics would be influenced by such a factor. To our surprise we found on completing the results that diabetics, irrespective of age, chose on the average a diet different from normal subjects. Secondly, we expected from previous results (8) that the absolute amount of some foodstuff would prove to be the factor of difference. In this again we were wrong. We, therefore, think that no appreciable error has been introduced by the psychological element in the investigation.

The quantitative method alone can elicit data concerning the diet in terms of absolute values and the significance of these absolute values will first be considered.

The ability of this method to yield accurate data regarding the total quantity of food consumed is largely invalidated by its incapacity to take into account the factor of appetite. The appetite at any particular time is influenced by present and preceding circumstances. It is common experience that a good appetite rarely accompanies a feeling of ill health, and for that reason subjects, whether non-diabetic or diabetic, who were conscious of being ill, were excluded from the investigation. The appetite at any particular time of subjects capable of taking their usual amount of food is largely determined by the amount of food they have previously obtained. Thus if a subject, just previous to investigation, has eaten a full meal he will tend to under-estimate his food requirements, whilst if his diet has been restricted for some days, hunger will prompt him to over-estimate his habitual capacity for food. This latter consideration applies especially to the diabetics of our series. The majority of them were not seen by us immediately symptoms appeared but were referred to us by their physicians from outside the hospital. Such patients had almost invariably received some vague instructions as to restrictions of their diet, with the result that, when we saw them a few days later, they were more or less hungry. If it is further remembered that hunger is one of the classical symptoms of diabetes mellitus, even when the patient takes an unlimited amount of food, it will be realised that circumstances combine to render the diabetic liable to over-estimate his food requirements. We are, therefore, not inclined to attach importance to our finding that diabetics choose diets of larger calory value than do corresponding subjects. It may well be that the diabetics prior to the onset of the disease have an innate tendency to overeat, but it may equally well be simply that

they were hungry at the time of investigation. At present we can only leave this point as an open question.

Judged by ordinary standards the calory values of the diets chosen are below the normal average. Cathcart and Murray (2) found that the average food intake of healthy subjects in a similar social class was about 3,000 calories a day. In our series the average intake for all normal controls was about 2,500 calories, and even the diabetics estimated their requirements at only 3,000 calories. We think this low intake is largely explained by an inherent defect of our quantitative method. The daily intake of food was estimated at one time, and thus the subjects were deprived of the natural stimulus to choice of quantity, namely, the appetite that normally develops in between meals. The estimated calory requirements are, therefore, probably lower than the actual calory value of the food eaten by the subject.

On one point only would the figures for the calory intake appear to be of significance. That is in their relation to age and sex. Males always chose more food than females of the corresponding group, younger subjects more than older subjects of the same sex. This can hardly be fortuitous.

The calory value of the diet is dependent upon the amount of fat, protein and carbohydrate chosen, and the objections which we have just shown to exist against accepting at face value the absolute calory values and the apparent difference between the caloric intake of diabetic and normal subjects, apply with equal force against the acceptances of the absolute values and the apparent difference of these values in the case of each of these foodstuffs. But there are some peculiar discrepancies between the absolute values of carbohydrate, protein and fat which suggest that the differences between the diabetics and normals may be dependent on more than those circumstances which influence the total amount of food chosen.

It has previously been pointed out that it is relatively easy to assess with some degree of accuracy the amount of fatty foods in the diet, whilst it is more difficult to obtain an accurate statement of the daily amount of carbohydrate ingested. This is largely due to the fatty foods being concentrated, satisfying to the appetite, and not such as to lend themselves to casual consumption. The absolute amount of fat in the diets is, therefore, more likely to be of significance than the absolute amounts of either protein or carbohydrate. Reference to Table III will show that the ratio $\frac{\text{difference between diabetics and normals}}{\text{standard error}}$ is less than 3 for

carbohydrate and protein in all the groups save that of females 46-75 years of age. In other words the difference between the absolute amounts of carbohydrate and protein consumed by diabetics and normals is not greater than could be accounted for by chance sampling. But the same ratio in the case of fat is in every case greater than 3 and thus the difference

between the absolute amount of fat chosen by diabetics and normals is outside the limits of chance error. A definite reason must lie behind this difference in preference for fat. Hunger may explain it, but there appears to be no reason why hunger in the diabetic should inculcate preference for fat rather than carbohydrate or protein. Indeed we have pointed out above that after development of the disease the diabetic's preference for carbohydrate seems to increase. We think, therefore, that the figures for fat definitely suggest that diabetics take a larger amount of fat than normal subjects.

It has been shown that information regarding the selected diets in terms of absolute amounts is open to criticism on the grounds that the amounts of food selected by a subject at the time of investigation is strongly influenced by the degree of appetite at that time. Such criticisms no longer hold when we come to consider the proportionate constitution of the diet. The relative proportion of carbohydrate, protein and fat are determined by the natural preference of the subject. This preference is independent of appetite and is the main factor in deciding the types of food available in the subject's household. When well established it colours the whole dietetic choice of a man. The subject who chooses fat bacon and fried potatoes at breakfast, chooses fat meat at dinner, thickly buttered bread at tea and cream whenever possible. A man who likes butter spread thickly on his bread will not choose to butter his bread thinly if he is not hungry, and neither will a man who likes jam suddenly develop a dislike to this food because his appetite is keen. The natural preference appears to express some inherent individual tendency and as such ensures that the proportionate composition of the diet remains constant.*

In the case of the quantitative method the proportionate composition of the diet is shown by the percentage calories derived from carbohydrate, from protein and from fat. For the normal control group the average proportion of calories from carbohydrate was 55.9%, from protein 12.3%, from fat 31.8% (Table II). Cathcart and Murray (2) by a more laborious and more exact method found that the diets of families in Cardiff and Reading of the same social class yielded an average of 57.0% of calories from carbohydrate, 10.3% from protein, and 32.7% from fat. The correspondence between these two sets of results is sufficiently close to suggest that our quantitative method gives a fair idea of the proportionate composition of the diet. Variations in proportionate composition of the diet are revealed by both methods of investigation and a comparison of the results yielded by the two methods will give some idea both of the agreement

* Temporary alterations in dietetic preference as a result of extraordinary external circumstances undoubtedly do occur, as for example the desire for carbohydrate food that develops after prolonged and exhausting muscular effort. But the subjects of this investigation were not exposed to such circumstances, they were passing a routine existence and under these conditions the individual dietetic preferences appear to remain the same.

between the methods and of the constancy of the dietetic differences in the different groups of subjects. The qualitative method (Table I) purely reveals the percentage of individuals in a group whose diet varied in composition from the average diet of the control group, whilst the quantitative method shows the variation from the standard of the individual diets.

A searching test of the agreement between the two tests can be made by comparing the results obtained on the individual diabetic patients, and in this connection it should be remembered that the results by each method were arrived at quite independently by two different observers. To effect the comparison the average proportionate composition of the diet for the group of normal subjects, as determined by the quantitative method (55.9% of calories from carbohydrate, 12.3% from protein, 31.8% from fat, Table II) was taken as the normal standard. Diabetics deriving more than the standard percentages of calories from carbohydrate were classified as those having a preference for carbohydrate, those deriving a greater percentage of calories from fat as having a preference for fat, and those whose taste was below or corresponded to the normal standard. It was found on comparing the estimated preferences arrived at by both methods in the same patient that complete agreement had been achieved in 78% of the cases, that in no case was there gross discrepancy, and that in the 22% of cases in which the two methods were not in agreement the discrepancies arose from a difference in opinion as to whether the proportion of fat or of carbohydrate was slightly increased or normal. With this agreement in mind we may proceed to consider the variations in composition of the diet as revealed by both methods.

To compare the variations in composition of the diet as shown by the two methods the average composition of the diet in any normal control group as determined by the quantitative method (Table II) is taken as the diet of standard composition for persons of that age and sex. The number of subjects in either the normal or diabetic section of this group, whose diet varies in any particular way from this, may then be expressed as a percentage of the total number of subjects in the section. Thus in the males aged 16-46 (Table II) the average number of calories derived from fat in the normal control group was 31.1%. Taking the figures for the individual patients it was found that 93% of the diabetics and 47% of the normal subjects chose diets yielding more than this percentage of calories from fat. The percentages of subjects for all the groups being determined, the figures for all the diabetics and all the normals were calculated. It was found that by the quantitative method 81% of the diabetics and 46% of the normals took diets containing proportion of fat greater than the average, whilst the qualitative method showed 76% of diabetics and 34% of normals with this tendency. Similarly, as regards carbohydrate, it was found that by the quantitative method 22% of diabetics and 47% of normals, and by the qualitative method 20% of diabetics and 34% of normals took more than the usual proportion of this foodstuff in their diet.

The results of both methods thus agree in the finding that the proportions of carbohydrate, protein and fat in the diet taken by the diabetic before the onset of the disease differs from the proportions in the diet chosen by comparable normal subjects. The figures given in Table II show that whilst the proportion of protein taken by both groups is approximately the same the proportions of fat and carbohydrate chosen by the two groups differ significantly.

It may, therefore, be concluded that the diabetic, prior to the onset of his disease, chooses a diet yielding a greater proportion of calories from fat and a smaller proportion from carbohydrate than do individuals who do not develop diabetes.

The significance of the results

The question now arises as to whether the development of diabetes mellitus in a particular subject is in any way influenced by the difference in dietary habits, which has been shown to exist between the individual who subsequently develops diabetes and the individual who remains free from this disease.

That this dietetic difference is not the only ætiological factor may be seen immediately. Heredity undoubtedly plays some part and according to White, Joslin and Pincus (12) the factor predisposing to the disease is inherited as a simple Mendelian "recessive" trait. In our present series of diabetics a history of diabetes mellitus in some blood relation was obtained in 30.0% of the cases, whilst in the 268 cases used in the two normal control series a family history of the disease was only encountered in 1.5% of cases.

The possibility suggests itself that there may be some connection between family predisposition to the disease and the type of diet preferred. Our figures, however, lend no support to this suggestion for those diabetics with a family history of the disease chose on the average diets which approximated a shade more closely to the normal standard, than did those diabetics with no such predisposition.

In a recent paper Joslin, Dublin and Marks (4) have established on a secure basis the general opinion of clinicians that overweight precedes diabetes mellitus in a large majority of cases. This finding is confirmed in the present series of diabetics, of whom 60.1% were overweight on first coming under treatment. Taking this association between obesity and the disease in conjunction with our results showing that potential diabetics prefer an excessive proportion of fat in their diets, it is difficult to avoid the impression that a diet containing an excessive proportion of fat plays some role in the ætiology both of diabetes mellitus and the preceding obesity. The data at present available do not permit a definite suggestion as to the importance of this role, and the question will, therefore, be left for discussion in another paper (Himsworth (9)).

Our results, however, were definitely significant in one direction. As the potential diabetic derives a diminished proportion of his calories from

carbohydrate, if it is assumed that the total calory value of the diets taken by potential diabetics and normal subjects do not differ widely, then the potential diabetic takes a smaller amount of carbohydrate in his diet than is normal. Taking 3,000 calories as the average daily intake of food for people in this social class (2) it can be calculated from Table II that in the groups of potential diabetics, a daily average of 382 g of carbohydrate is ingested, whilst the normal subjects eat 420 g daily. Now it has been shown by one of us (H P H (8)) in a previous paper that the sugar tolerance and insulin sensitivity of a healthy individual is determined solely by the amount of carbohydrate ingested daily, and reference to the charts given in that paper will show that the sugar tolerance and insulin sensitivity on a diet of 382 g are approximately 20% lower than they are on a diet of 420 g*. When one considers the great decrease in tolerance in the diabetic such a small decrease as results from this dietetic difference seems relatively small, but it is at least of significance that the diet chosen by the potential diabetic is one, that of itself, tends to decrease sugar tolerance and insulin sensitivity. It is possible that in the course of months or years the persistent operation of such a dietary factor curtailing sugar tolerance and sensitivity to insulin may lead to progressive and permanent impairment of the individual's capacity to deal with carbohydrate so that finally diabetes mellitus appears. One thing is evident and that is that the diabetic, prior to the onset of his disease, chooses a diet which causes an approximation of his carbohydrate metabolism to that seen in diabetes mellitus.

Evidence has, therefore, been obtained in support of the hypothesis which this investigation was designed to test, namely, that the diet of the diabetic, prior to the appearance of the disease, is one which in the non-diabetic subject impairs insulin sensitivity and sugar tolerance.

SUMMARY

1 The diet of 143 diabetics prior to the onset of their disease has been compared with the diet of two comparable groups of normal subjects containing 137 and 121 individuals respectively.

2 Two methods have been used in eliciting the nature of this diet. One, the qualitative method, which by questioning aimed at discovering if the diet differed from the normal, the other, the quantitative method in which the subjects, from foodstuffs of known composition, chose a day's intake in food, which was then expressed in terms of carbohydrate, protein and fat.

* The change in sugar tolerance that occurs in a normal subject as the result of increasing the carbohydrate in the diet from 50 g to 425 g was arbitrarily chosen as 100% increase in sugar tolerance (H P H (8)). It is to this scale of percentage values that reference is made here.

3 Both methods reveal that the majority of diabetics, prior to the onset of diabetes, prefer diets containing an excessive proportion of fat, and that a smaller number of diabetics than normal subjects prefer diets containing an excessive proportion of carbohydrate foods

4 It is shown that the diabetics chose diets of greater calory value and containing larger amounts of carbohydrate, of protein and of fat It is indicated that this increased consumption arises possibly from an error inherent in the method used The difference between the diabetics and normal subjects in the amount of fat consumed is, however, from a statistical point of view, so much greater than the difference in consumption of carbohydrate and of protein, that significance may be attached to it

5 The diet of diabetics before the onset of the disease, in comparison with the diet of normal subjects contains the same proportion of protein, a diminished proportion of carbohydrate and an increased proportion of fat

6 It is pointed out that similar diets impair sugar tolerance and insulin sensitization in non-diabetic subjects, and that the ingestion of such a diet by a potential diabetic would favour the appearance of the disease It is suggested that the habitual ingestion of a diet containing a diminished proportion of carbohydrate may cause progressive permanent impairment of sugar tolerance and insulin sensitivity so that, in the course of time, diabetes mellitus results

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DIET AND THE INCIDENCE OF DIABETES MELLITUS

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IN a previous paper by Himsworth and Marshall (22) it has been shown that diabetic subjects, before the development of their disease, choose diets containing a smaller proportion of carbohydrate and a greater proportion of fat than do normal individuals. Since diets of similar composition to those chosen by diabetics have a deleterious effect upon sugar tolerance and insulin sensitivity of healthy men, as compared with equicaloric normal diets (21), the suggestion was made that the composition of the diet might be an influential factor in the ætiology of diabetes mellitus. The weakness of this suggestion lies in the retrospective nature of the evidence upon which it is based. This evidence showed that diabetics, before the onset of the disease, chose diets differing from those of normal individuals, but it did not show that if the normal individuals had been given these "abnormal" diets a considerable proportion of them might have developed diabetes. It might alternatively be that subjects predisposed to diabetes have, incidentally, dietetic preferences of this characteristic type. As a direct proof of the validity of the suggestion is obviously impossible, the decision between these two alternative explanations of the dietetic difference can only be furthered by an appeal to circumstantial evidence, and the most promising line of investigation would appear to lie in a comparison of the incidence rate of diabetes in various large groups of people and of the differences in dietary characteristics of each group. If it can be demonstrated that there is an association between the standard diet of a population and the incidence rate of diabetes, or that in a particular population, change in the composition of the standard diet is associated with change in the incidence of diabetes, and that the differences in diet in various groups of the same population are reflected in corresponding differences in frequency of diabetes, then, the suggestion that the dietetic idiosyncrasies of the potential diabetic are of no significance becomes highly improbable.

In this paper an attempt will be made to summarise the available evidence on these points and to discuss the possible conclusions that it suggests.

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Preliminary consideration of the data

As diabetes mellitus is not a notifiable disease there are no figures available showing its incidence in different countries. To obtain an idea of the national incidence rate it is, therefore, necessary to rely on the diabetic mortality rate in that country. These rates are expressed as the number of deaths from diabetes for each 100,000 living persons.

In a recent paper Joslin, Dublin and Marks (27) have shown that the diabetic death rate is increasing steadily all over the world (Fig 1), despite the great improvement in treatment since the introduction of insulin.

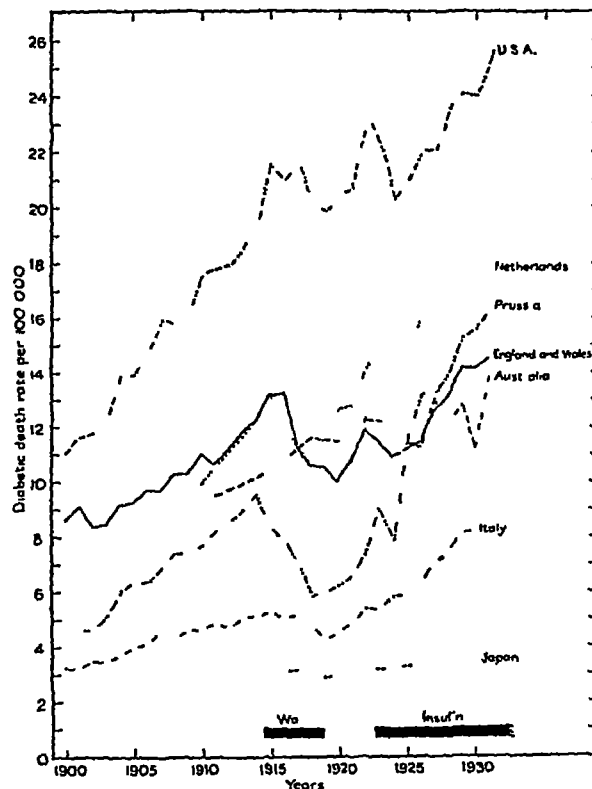


Fig 1 Showing the increasing mortality rate from diabetes mellitus in some of the principal countries of the world (26) (27) (40)

At first sight it may appear that the difference in diabetic mortality rate between different countries and the rising mortality rate in particular countries may be explained on the grounds of the relative degrees of efficiency in the national medical services and by the more accurate registration of deaths from diabetes during the last few years. Such an explanation, however, hardly explains the different diabetic death rates of the different

capitals or of contiguous countries. For example for the year 1922 the death rate in Tokyo was 2.4, in London 9.5, in New York 27.8 per 100,000, in 1928-29 the rate in the States of New Hampshire, Vermont and Maine averaged 25.5, whilst across the Canadian border in Quebec the rate was 11.0 (1921-26). It is impossible that the standards of medical competence in these places should vary so enormously as to produce such different rates. It may be concluded, therefore, that the registration returns with their evidence of a rising diabetic death rate in many countries are reliable as a proof of increasing incidence of the disease, and this conclusion receives the support of the American workers (27).

When insulin first came into general use in 1922-23 a slight reduction of the mortality rate was produced but from then on the death rate continued the steady climb which was apparent in the pre-insulin era. Naturally the full benefits of insulin treatment were not attained in the first years of its use, and even now improvement in its therapeutic application appears still to be in progress. This is shown by the progressively increasing span of life between onset of the disease and death in fatal cases of diabetes. Thus in Joslin's experience (28) the average duration of life in fatal cases has increased from an average of 7.6 years in the period 1922-26, to an estimated average of 10 years in 1934. The average duration of life in diabetic patients is increasing, and yet the mortality rate from the disease is rising rapidly. It can only be concluded that the disease is increasing in frequency even more rapidly than is indicated by the rising diabetic mortality rate, and an assessment of the national incidence of diabetes will, therefore, be too low if this is taken as approximately identical with the diabetic mortality rates. It is, however, a just assumption that countries which are sufficiently well organised to produce detailed mortality statistics, have standards of efficiency in medical treatment which do not, on the average, differ materially. If this assumption is allowed then the annual proportion of fatal to living cases of diabetes in the various countries considered will be approximately the same, the diabetic mortality rates will reflect the diabetic incidence rate, and a comparison of the national mortality rates will indicate the relative frequency of diabetes in the different countries. The various national mortality rates cited in the present paper are used with this significance.

Details of the diets eaten by different races, nationalities and social classes are necessarily fragmentary and, therefore, comparison between them must be made with considerable caution.

Dietary studies have been carried out from time to time in most countries in the world but the most careful and frequent studies have been made in Europe and North America. In these latter countries dietetic data are available for different social classes and the diet is found to vary considerably with the economic status of the individuals concerned. It is necessary, therefore, to decide what social class shall be taken as representative of the general dietary habits of a country. The most suitable class appears to be

that of manual workers including all grades from the semi-skilled labourer to the artisan. This class constitutes the majority of a country's citizens and it is their tastes and preferences which to a large extent determine commodity prices. The higher social classes can buy what they like in the matter of diet, but the class of manual workers, whilst removed from penury, are, by financial pressure, restricted to those foods which are cheapest. The diet of the manual workers, therefore, can be taken as more truly representative of the national diet than that of classes whose choice is either confined by poverty or is unrestricted by reason of affluence. For this reason the comparison of national dietaries is restricted to that of the dietaries of manual workers in the different countries, unless it is specifically stated otherwise.

The laborious nature of the investigations required to obtain reliable information on the food intake of groups of people has generally resulted in these studies being confined to small groups of individuals. In such groups individual variations in appetite cause considerable variation in the amounts of the different foodstuffs taken. For this reason comparison of different diets on the basis of amounts is very unsatisfactory, and when one considers that the individuals studied are only a very small number of a large social class, any attempt to compare national diets on the basis of these figures becomes hazardous. It is only in the case of extreme differences, such as those between European and Japanese diets that any significance can be attached to such comparisons. The proportions of the different foodstuffs in the diet, however, provide a surer basis of comparison. If one takes a series of results from one social group giving diets of widely differing calory values (9) (47) it will be found that although the amounts of the different foodstuffs vary widely the proportions are relatively constant. Comparison between the different diets in this paper has, therefore, been made on the basis of their proportionate compositions and this is most conveniently expressed as the percentage of calories derived from carbohydrate, from proteins and from fat.

The proportion of dietary protein remains remarkably constant although the amount of protein taken varies directly as the calory value of the diet. Despite the wide range of composition in the diets of different races and despite the change in dietary habits that has occurred during this century, the diets chosen by different peoples and at different times, are all such as to contain about 12% of the total calories in the form of protein. Changing tastes, racial habits, and social differences influence the type of diet by causing alteration in the proportions of dietary carbohydrate and fat selected. The percentage of protein calories remaining constant, it follows that the percentages of carbohydrate and of fat calories are in inverse relationship, so that, either may be used to express the type of diet under consideration. It should thus clearly be understood that, in the succeeding discussion, a rise in the percentage of calories derived from fat always implies a corresponding fall in the percentage derived from carbohydrate and *vice versa*.

The relationship of diet to national differences in the incidence of diabetes mellitus

The greatest recorded difference in the mortality rate from diabetes mellitus is between the United States of America and Japan. In 1930 the former had a rate of 24.0 and the latter of 3.5. That there are great differences between the diets of the two countries is common knowledge. American diets contain a high proportion of fat and a low proportion of carbohydrate whilst Japanese diets are characterised by a very low proportion of fat and a high proportion of carbohydrate. Toda in 1927 (58) stated that Japanese diets yield about 5% of calories from fat and 80% from carbohydrate.

TABLE I

Table showing that the typical diet of different countries bears a relation to the diabetic mortality rate, those countries in which the diet contains a high proportion of carbohydrate having low rates and those with a low proportion, high rates. It should be noted that the calory value of the diet bears no relation to the diabetic death rate.

Country	Year	Diabetic death rate for 100,000 living	DIET		Calory value	Year	Reference
			Percentage of calories — from fat	from carb			
United States of America	1920	20.4	36.1	50.8	3,175	1920	Pearl (48) urban working families
Holland	1930	17.6	35.5	53.0		1932	Banning (5) urban working families
England and Wales	1931	14.5	32.0	58.0	3,000	1931	Catheart and Murray (9) working families Cardiff and Reading
Scotland	1921	10.1	28.3	57.2	2,466	1921	Tully (59) working families with mean " income over 12/ a week
Italy	1930	8.2	18.2	65.3	2,450	1933	Agnallo (1) urban working families
Japan	1919	2.9	4.7	85.0	3,766	1919	Kobo and Sokamoto (31) workmen

a figure which is in agreement with previous surveys of the last 50 years (14) (24) (31), whilst in 1930 prisoners in Middle West penitentiaries were allowed diets yielding 38.1% calories from fat (23). When it is realised, as will be shown later, that fatty diets are in most countries the privilege of the rich, then the American allowance of fat for prisoners acquires more significance as a reflection of a popular taste for diets rich in fat. An inspection of previous dietary studies in America (48) confirms the existence of this preference. In this respect it is significant that Atwater, in America, in the early years

of this century stated that a standard diet should contain 54% of carbohydrate calories and 35% of fat calories, whilst Rubner about the same time estimated the standard European diet as containing 67% of carbohydrate calories and 16% fat calories (*see* Lusk (34) p 447)

The diabetic mortality rates for the other principal countries of the world lie between the above extreme rates, and dietary surveys show that the different national diets lie between the extremes of the American high-fat low-carbohydrate diet and the Japanese low-fat high-carbohydrate diet. In Table I comparison is made between the national diabetic death rates and the typical diet of urban working families in the particular countries. In the examples chosen the different countries are graded by mortality rate and it will be seen that a high death rate from diabetes is associated with diets containing a small proportion of dietary carbohydrate and a high proportion of dietary fat. It can incidentally be seen (Table I) that no correlation exists between the total calory value of the diet and the diabetic mortality rate.

It would be laborious to confirm here this association between the incidence of diabetes and the national diet by examining all the available evidence in detail, but in Fig 2 an attempt has been made, using many data of different nations, to demonstrate this association in a form that can easily be appreciated. In this figure the percentage of calories from carbohydrate used by urban working class families in each country, is charted against the corresponding diabetic death rate of that particular nation for the year in which the dietary survey was made. Thus in the case of the United States of America the death rate, 17.6, is plotted against the percentage of calories from carbohydrate, 50.8%, which is taken from the dietary survey by Pearl in 1920 (48) (Table I).

The attempt to correlate the diabetic death rate of a country with the dietetic habits of a small number of its people must necessarily involve a large margin of error, but despite this the correlation appears to be astonishingly close. It will be seen from Fig 2 that the points charted fall approximately on a hyperbolic curve and that the trend of this curve indicates that the countries with a high death rate from diabetes are those in which the inhabitants prefer diets containing a small proportion of carbohydrate (and a high proportion of fat), whilst the countries with a low diabetic mortality are those in which diets containing a high proportion of carbohydrate (and a low proportion of fat) are chosen.

In view of this association the possibility may suggest itself that the diabetic mortality of the Eskimos and the inhabitants of countries like Labrador should be very high. But the popular assumption that they take a very high-fat low-carbohydrate diet is false. Dietary studies by Mitchell (44) in Labrador show that the inhabitants choose diets yielding approximately 70% of calories from carbohydrate and 21% from fat, Heimbecker (18a) from studies on Eskimos living in primitive conditions on Baffin Island gives their diet as containing 8.2% of carbohydrate and 47.6% of fat calories, and

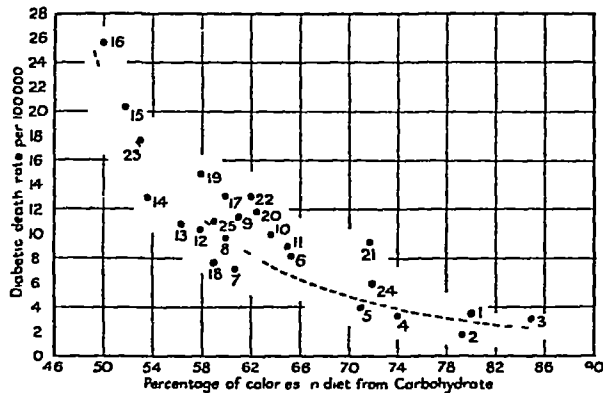


Fig 2 Diagram showing the relationship between diabetic mortality rates and the percentage of calories derived from carbohydrate in the diets at different times and in different nations. The numbers above the points on the curve refer to the key which is given below. These key numbers are in the left hand column, in the next column is the country concerned, in the third column the diabetic death rate for this country in the year nearest to that in which the dietary study was made, in the fourth column the actual year of the dietary observations, and in the last column the number in the list of references, at the end of this paper, of the publication containing the dietary study.

Key No	Country	Diabetic death rate	Dietary study	
		Year	Year	Reference
1	Japan	1910	1909	24
2	"	1920	1919	31
3	"	1927	1927	58
4	Italy	1900	1894	41
5	"	1905	1906	1
6	"	1930	1934	2
7	Scotland	1900	1900	46
8	"	1910	1911	32
9	"	1915	1915	16
10	"	1917	1917	16
11	"	1918	1918	16
12	"	1921	1921	Av 47, 50
13	"	1924	1924	47
14	"	1931	1931	9*
15	U S A	1920	1920	48†
16	"	1931	1931	25
17	" (Atlanta)	1929	1931	23
18	Switzerland	1915	1912	17
19	England and Wales	1931	1931	8
20	" "	1924	1924	47
21	Holland	1910	1907	5
22	"	1915	1916	5
23	"	1930	1930	5
24	Prussia	1917	1917	6
25	"	1918	1913	15

* Average of classes with income of from £3 4s 6d to £4 0s 2d

† Average of classes with income of from \$2,000 to \$2,500

Thomas (57) states that the Eskimos themselves eat little fat. These figures for fat calories are no greater than those given for modern American diets. Apparently in these cold regions fat is too precious for food and must be saved for making oil, curing pelts, etc. The incidence of diabetes amongst these races is unknown, but it has not been sufficiently high to excite comment.

Change in the national diabetic mortality rate in relation to change in the national diet

It will be seen from Fig. 1 that from the year 1900 to the year 1931 a rise in the diabetic mortality rate has occurred in the principal countries of the world. In the majority of the countries this rise is interrupted at two places, during the years of the Great War and in the years shortly following the introduction of insulin into general medical practice. The relation of the general upward trend of the mortality rate to the change in the dietetic habits of various countries will first be considered, and then the association between the fall in diabetic mortality during the war years will be correlated with the enforced changes in diet consequent upon war conditions. The reason for the fall after the introduction of insulin requires no discussion.

During the last 30 years a steady change has been occurring in the dietary habits of the countries of the western civilisation. The change has been manifested in the choice of diets with a gradually decreasing percentage of calories derived from carbohydrate and a gradually increasing percentage from fat but with little change in the total intake of food. The alteration in diet is indicated clearly by figures available for England and Wales. In 1904 the Board of Trade produced figures showing that the "man value" of the diet in city workmen's families was such as to yield 3,094 to 4,013 calories, of which 71.0% to 65.7% were derived from carbohydrate and 17.6% to 23.2% from fat (12)*. In 1928 Cathcart and Murray (8) carried out a dietary survey of working-class families in Cardiff and Reading and found that the diets yielded on the average 3,000 calories with a derivation of approximately 58% from carbohydrate and 32% from fat. In 1911-12 Rowntree (53) found that English agricultural workers took diets averaging 2,702 calories and yielding approximately 73% of calories from carbohydrate and 19% from fat, whilst in 1923 Hill (20) showed that similar subjects chose diets yielding 2,872 calories and containing 65% of calories from carbohydrate and 22% from fat. Other dietary studies made in other years bear out the dietetic tendency revealed by these results.

The most complete results available are from Scotland. In Glasgow dietary surveys have been made at fairly frequent intervals and as they were all carried out on the same class of the population we have a fairly complete record of the change in the dietary habits of the urban population of Scotland until 1924, and the sequence can be carried up to 1930 by using the figures from similar families in the St. Andrew's survey of that year. From 1900

* The figures are given as recalculated by Dunluce and Greenwood (12)

to 1930 the proportion of fat in the diet increased from 25.5% to 33% and the proportion of carbohydrate decreased from 61% to approximately 53%, whilst the daily caloric intake remained at about 3,100. This changing diet of Scottish families is shown in Fig. 3 in relation to the diabetic death rate, and it will be seen that with the steadily rising death rate the proportion of dietary fat rises and of carbohydrate falls.

In Holland similar studies have been made by Banning (5) on working-class families in the town of Zaandam. In 1907 the percentage of calories from carbohydrate was 72%, and in 1916, 62%, in 1930, 53%. The percentage of calories from fat was in 1907, 17%, in 1916, 26%, in 1930, 35.5%. The death rate from diabetes changed from 9.9 in 1910, to 13.1 in 1915 and to 17.6 in 1930.

In the United States of America, Pearl (48) from a study of the total food consumption over the years 1911 to 1918 arrived at a similar conclusion. He found that there had been no increase in the "per capita" food consumption, but that "the greatest relative advance in consumption was in respect of fat" (48, p. 221).

From Fig. 1 it can be seen that in the last 30 years the diabetic death rate has changed hardly at all in Japan, and in this time the working-class diet has undergone no significant change. In 1886 Eijkman (14) found that prisoners derived an average of 3.9% of their calories from fat and 84% from carbohydrate, in 1919 Kobo and Sokamoto (31) found workmen's dietaries to yield 4.7% of the total calories from fat and 84.9% from carbohydrate, and Toda (58) in 1927 said that the Japanese diet still contained about 5% of calories from fat and 80% from carbohydrate.

It can, therefore, be concluded that any rise in the diabetic death rate during the last 20 years has occurred concurrently with a change in dietetic preference which led to diets containing a progressively larger proportion of fat and a progressively smaller proportion of carbohydrate. In all cases the total intake of food appears to have remained at approximately the same figure.

The effect of the Great War on the diabetic death rate is shown in Fig. 1. From this figure it will be seen that the rate fell in those countries in which the food supply was affected by the war and did not change in those in which the food supply was independent of the blockades. Thus Japan and Australia had a steadily rising death rate through the war years and Italy, a practically self-supporting country as regards food, showed little change. But countries situated nearer the main theatre of war show a fall whether they were actual belligerents or neutrals supplying food to the Central Powers, as was the case with Holland and Denmark. The time relations of the fall in rates are of interest (Figs. 1 and 4). Thus the fall was apparent in Prussia in 1915 whilst it was not evident in England until 1917. It will be remembered that a strict naval blockade of Germany was enforced from the outbreak of the war, whilst the submarine blockade of England did not become really effective until the spring of 1917. Further, the fall in diabetic mortality

in the United States of America did not occur until 1918 when the use of foodstuffs had become restricted by high prices and government regulations (27) (48)

In Fig 3 are shown the effects of the war on the diabetic death rate and type of diet available in Scotland The death rate fell from 11.4 in 1915 to

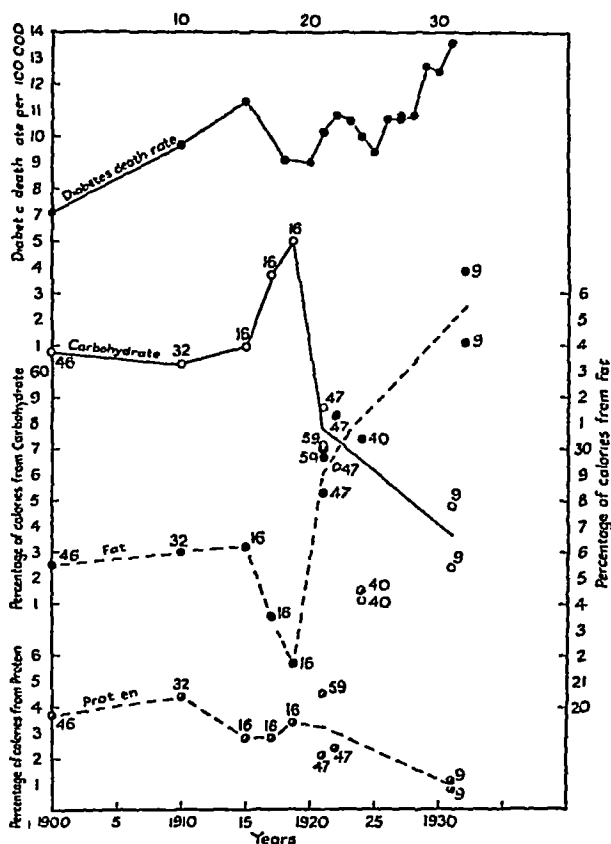


Fig 3 Diagrams showing the relationship of change in the diabetic death rate of Scotland to change in dietary preference The figures over the points showing the percentage of protein carbohydrate or fat indicate the reference to the dietary studies The diets charted under reference 9, however, refer only to the mean value of those diets in Cathcart and Murray's study which were obtained from individuals of a similar economic station to those from whom the other dietary data in this diagram were obtained, i.e., to the families having weekly incomes between £3 4s 6d and £4 0s 2d

9.0 in 1920 During this period dietary studies were made by Ferguson (16) In 1915-16 food was still plentiful and she found that working-class families in Glasgow were taking 61% of carbohydrate and 26.2% fat (calory value 2,890) In 1917 the food shortage began to be felt and the diets chosen by the same families now contained 64% of carbohydrate calories and 23.5% of fat calories (calory value 2,661) In 1918 when the food supply was

rationed the figures had changed to 65.0% from carbohydrate and 21.7% from fat (calory value 2,680). It should be noted that the calory value of the diets changed little and are not much different from those found in studies before and some years after the War.

Naturally the food shortage was felt most acutely in the towns. Here food restrictions were capable of rigid enforcement, and if the change in diabetic death rate is related to the change of diet then the change in rate in different cities should be proportional to the severity with which the food supply was restricted. In Fig 4 are shown the mortality rates for

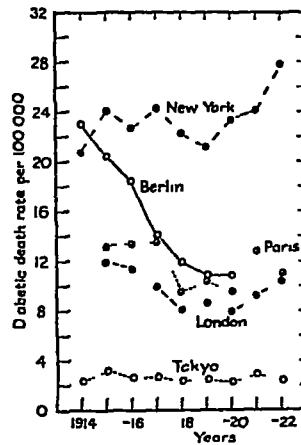


Fig 4 Diagram showing the effect of the Great War on the death rate from diabetes mellitus in New York, Berlin, London, Paris and Tokyo (26)

New York, Berlin, Paris, London and Tokyo. It will be seen that in Tokyo, where food was unaffected by the war, the death rate remained unchanged, and that in New York which was but little affected a slight fall in death rate commences in 1918. In Paris and London in which the food available at different times varied to the same extent a fall of rate of about 4 is shown, but in Berlin where the restrictions were early and severe the rate falls from 22.5 to 10.8. In each case the fall in rate naturally lagged somewhat behind the dietary limitations and persisted for some time after the restrictions were lifted.

Information is available regarding the diets allowed in German towns during the war. In 1912-13 the Eltzbacher Commission (15) was set up to consider the allowance of food required if the population of Germany were to be kept in good health. This Commission before the war recommended a diet containing 26% of calories from fat and 59% from carbohydrate (calory value 4,777). Actually in the winter of 1916-17 the civilian rations in Bonn contained 70% of calories from carbohydrate and 12.5% of calories from fat with a calory value of 1,510 (56). This figure for the calory value would appear to be unusually low, and Loewy (33) for the same year gives

the civilian diets in Berlin as containing 2,275 calories with 11% of fat and 47% of carbohydrate. The army was allowed 20% of fat calories and 62% of carbohydrate calories (calory value 3,025) (6). Later that year the allowance for labourers doing moderate work was 14% of fat and 72% of carbohydrate (calory value 2,051) (6). As regards the total calory value of the diet, Starling (56) computes that workmen received up to 3,000 calories a day, and their dependents much less.

An interesting point is brought out by a study of the urban and rural death rates during the war period in Prussia (49). These are shown in Fig 5 and it will be seen that the reduction in mortality in the towns is very much more than in the country. Starling (56) in his report on the food conditions in Germany during the war throws an interesting light on this difference. Apparently the efficiency of the government mechanism for food distribution

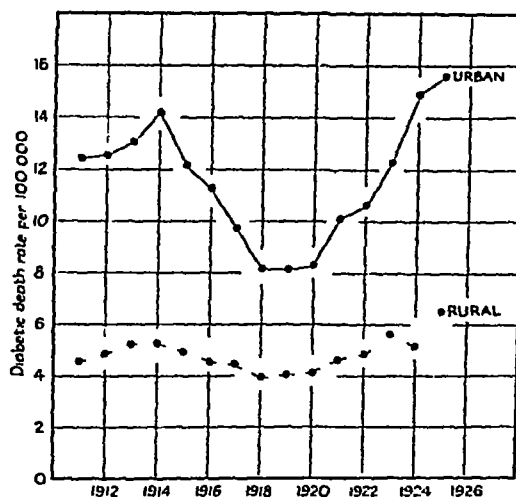


Fig 5 Diagram showing the effect of the Great War on the urban and rural diabetic mortality rates in Prussia (49)

was impaired to the point of breakdown by the non-co-operation of the farmers and market gardeners. The German government estimated that 25% to 33% of the food produced in the country was held back for illicit trade and private consumption, and there can be little doubt that through these illicit supplements the diet of the rural population changed relatively little during the war. It is significant that the rural diabetic death rate also changed little.

It may be concluded that the diabetic death rate, during the war, fell in all countries whether belligerent or neutral, in which the food supply was affected by the hostilities, whilst in those countries in which the usual supply of food remained available, the rate was unaffected. The dietary change associated with a fall in mortality rate was one yielding a diet with an increased proportion of calories from carbohydrate and diminished proportion

from fat. Change in the proportion of foodstuffs involved also reduction in the calory value of the diet, though in Great Britain this reduction was slight. It can also be seen that the reduction in diabetic death rate was proportional to change in the diet. The greater the proportion of carbohydrate in the diet, and the smaller the proportion of fat the greater the reduction in mortality.

Variations in diabetic mortality in relation to local dietetic conditions

It is well known that the diet of the rural population differs from that of the urban population of the same country, and it is of interest to note that the diabetic mortality rates also vary. In Table II urban and rural

TABLE II

Table showing the difference between urban and rural mortality rates from diabetes mellitus in U.S.A., Denmark, England and Wales (28) and Prussia (49). The rural rate for England and Wales is higher than the urban, but when this is corrected for age and sex distribution it is found to be lower (28).

Year	U S A		Prussia		Denmark		England and Wales	
	Urban	Rural	Urban	Rural	Urban	Rural	Urban	Rural
1920	10.4	13.1	8.2	4.1	14.5	11.0	9.9	10.4
1921	20.2	13.6	10.1	4.6	17.8	11.9	10.5	12.0
1922	22.4	14.9	10.6	4.8	20.2	11.2	11.7	12.8
1923	21.9	14.3	12.3	5.6	16.6	12.5	11.3	12.0
1924	20.2	13.4	14.9	5.1	16.2	9.8	10.8	12.0
1925	21.1	13.1	15.6	6.5	16.2	10.8	11.0	12.1
1926	22.6	13.9	14.9	5.6	14.3	12.1	11.3	12.8
1927	22.4	13.3	18.0	7.5	15.4	11.2	12.6	12.9
1928	24.6	14.4	18.8	7.1	15.5	11.7	12.9	14.4
1929	24.2	14.2			15.8	11.2	14.1	14.8
1930					16.8	12.7	14.3	14.2
1931					18.6	13.9	14.4	15.2

death rates for the United States of America, Prussia, Denmark and England and Wales are given for the years 1920 to 1931. These figures represent the crude death rates and when it is remembered that diabetes mellitus is much more common in old than in young people, it will be realised that in a country such as England and Wales, where the rural is of greater age than the urban population, death rates uncorrected for age distribution may give an erroneous impression of the relative mortality of the two populations. In Table II the figures for England and Wales differ from those of the other

three countries in showing a higher rural than urban diabetic mortality rate, but when this crude rate is corrected for age and sex it falls into line with the rural rate in other countries (28). Similarly in Table III when the crude rates for the four American States showing higher rural than urban crude rates are corrected the rural rate is found to be below the urban. It may be taken, therefore, that the rural death rate from diabetes mellitus is consistently below the urban rate.

Dietetic studies on rural populations have been carried out in America and in England and Wales. In 1903 Atwater (3), in America, found that farmers took diets yielding 55% of carbohydrate calories and 34% of fat calories whilst business men had diets containing 50% of carbohydrate and 37% of fat calories. The calory value of the diets was approximately the same, averaging 3,767 calories for the farmers and 3,678 calories for the

TABLE III

Table showing the diabetes mortality in urban and rural areas of U.S.A. expressed as the mean death rate per 100,000 white persons for the year 1928-1929 (28)

State	Total	Urban	Rural	State	Total	Urban	Rural.
All States	19.0	24.4	14.3	Washington	18.2	23.9	14.0
*Rhode Island	26.9	26.0	27.4	Oregon	17.5	22.4	14.6
*New York	26.7	28.2	21.3	Montana	16.6	23.1	13.1
*New Hampshire	26.0	25.6	26.4	Utah	15.9	23.1	11.5
*Vermont	25.5	41.9	22.6	Colorado	15.5	20.0	12.6
*Maine	25.1	31.5	22.6	North Dakota	15.4	29.4	14.0
Illinois	23.6	26.2	19.6	Florida	14.5	19.2	12.3
*New Jersey	23.3	27.3	17.7	Nevada	14.4	17.1	13.7
*Connecticut	23.0	24.8	17.8	†Louisiana	13.2	24.2	7.8
*Massachusetts	22.7	23.3	19.7	Kentucky	12.6	27.5	9.0
*Pennsylvania	22.6	26.8	18.6	†Virginia	12.6	17.6	11.0
*Maryland	22.5	27.1	16.7	Idaho	12.3	27.0	10.9
Nebraska	22.3	30.7	19.7	Wyoming	12.2	11.1	12.4
Delaware	21.4	25.8	17.4	†Georgia	11.5	19.1	9.4
Indiana	21.3	23.2	19.9	†South Carolina	11.1	25.4	8.0
Ohio	21.3	22.8	19.5	†Mississippi	10.7	21.2	9.4
Wisconsin	20.8	25.4	17.6	†West Virginia	10.3	18.1	8.4
Kansas	20.6	25.8	18.8	†Tennessee	10.1	19.1	7.9
Missouri	20.6	27.0	16.3	†Alabama	9.9	18.8	7.9
Minnesota	20.1	22.1	19.0	New Mexico	9.6	23.4	8.6
Michigan	19.3	19.1	19.5	†North Carolina	9.5	18.3	8.0
Iowa	19.1	24.5	17.0	Oklahoma	9.2	14.5	7.0
California	19.0	21.5	15.6	Arizona	8.8	17.0	6.8
				†Arkansas	8.3	17.7	7.4

business men. The diabetic mortality rate, for that year, in the States in the registration area was 13.0 in the urban and 12.1 in the rural population. Pearl (48) in 1920 carried out another survey in the same country and found farmers took diets yielding 56% of carbohydrate calories and 33% of fat calories, whilst a comparable urban group (teachers, professional men, engineers and salesmen) with an annual income ranging from \$2,150 to \$2,527 chose diets yielding an average of 50% of carbohydrate and 37.3% of fat calories. The calory value of the farmers' diet was 3,640 and of the

urban groups 3,181 The urban death rate in 1920 was 19.4 and the rural 13.1. Note should be taken that the rural diets were of higher calory value than the urban.

In England and Wales, in 1903, Dunluce and Greenwood (12) found agricultural labourers taking diets containing 65.0% of carbohydrate calories, 24.6% of fat calories, and having an average calory value of 3,646. Rowntree (53) in 1911-12 on another group found diets of 73% carbohydrate calories and 19% fat, with a total calory value of 2,702, whilst Hill (20) in 1923 found similar families in Essex taking diets with 65% carbohydrate calories and 22% fat calories in a diet of 2,872 calories. An economically comparable urban population in Glasgow was found by McNae (40) in 1924 to be selecting diets containing 51% carbohydrate calories and 30.4% fat calories and with an average calory value of 2,547 calories.

TABLE IV

Table showing the mean crude death rate per 100,000 for the years 1921-1926 for the provinces of Canada (42)

State	Deaths from diabetes per 100,000 population
Prince Edward Island	10.6
Novo Scotia	11.1
New Brunswick	11.1
Quebec	11.0
Ontario	11.9
Manitoba	8.2
Saskatchewan	6.2
Alberta	8.0
British Columbia	11.0

These examples will suffice to show that rural populations choose diets of approximately the same calory value as urban but which differ in containing a higher proportion of calories from carbohydrate and a smaller from fat, and also that rural populations have a lower death rate from diabetes than similar urban communities.

Apart from the rural and urban differences in diabetic death rates, differences occur in different localities in the same country. This is most strikingly brought out in North America. In Table III are given the diabetic mortality rates for 1928-29 in the registration States of the United States of America and in Table IV the rates for Canada for 1921-26.

It will be seen that as one proceeds north from the Gulf of Mexico the diabetic mortality steadily increases until one crosses the Canadian border. Then the rate drops sharply.

The average death rate from diabetes for 1928-29 in the United States was 19.0 for the general population, 24.4 for the urban population (Table III). Taking the ten Southern States which have been longest settled (marked † in Table III) it is found that none have a death rate which reaches the average for the whole country. The average general rate for the ten is 11.0 and the urban rate 19.9. In the ten northern Atlantic states (marked * in Table III) the average general rate is 24.4 and the urban rate 28.3. Crossing the Canadian border the average general rate falls to 12.0 in 1928. If geographically contiguous states in Canada and U.S.A. are considered then it will be found that whilst the rate in Quebec in 1926 was 11.0 the average of the rates for Maine, New Hampshire, Vermont and New York was 25.8 in 1928-29. It is obvious that the diabetic death rate is not a question of latitude, and the differences between contiguous states show that it is not a matter of climate. The possibility that race may play a part suggests itself but is immediately rejected from a consideration of the rates in the white and negro populations of the U.S.A. In the Southern States we have the opportunity of studying two completely different races living under similar conditions, and ideally constituted each to act as a control group for the other. It used to be said that American negroes were relatively immune to diabetes but in the five-year period ending in 1930 the mortality for coloured persons was very little lower than that of the white race (27). In Table V are given the figures from the American registration areas in which classification is made into "white" and "coloured". It will be seen that the diabetic mortality rates vary in the same way in each locality, and that both races conform to the general observation in U.S.A. that the farther north they are domiciled the greater the incidence of diabetes. Further it can be seen from Table V that for coloured, as for white races, the urban rate is greater than the general rate for the whole state. It is, therefore, clear that the factor determining the incidence of diabetes in the different States of North America is not race.

Dietary studies from the prisons of two of the Southern areas are available. Thus men in the prison at Atlanta, Georgia, were allowed, in January, a diet of 4,006 calories containing 27.9% fat calories and 59.7% carbohydrate calories (23), and the death rate in Atlanta was 13.1 "white" and 14.2 "coloured." Men in the Kansas prison of Fort Leavenworth in the same month were allowed a diet of 4,197 calories containing 32.5% of fat calories and 52.8% of carbohydrate calories (23), and the diabetic death rate in Kansas City was 19.9% "white" and 22.3% "coloured." Figures for the diets of negroes in the Northern States are not available but Rosenthal (52) has collected general information on this subject. He sent questionnaires to negro institutions in Louisiana, Alabama, North Carolina and Texas. The replies showed that the negro diet in the South consisted mainly of carbohydrate and that "meat, butter, milk and eggs were eaten in minimal quantities." Then "when the coloured persons came to the North their standard of living was immediately elevated," they received

higher wages for the same work as that done in the South, and it was found by an enquiry in Chicago that "their consumption of meat, milk, eggs and butter approaches and to some extent surpasses that of white persons" It would appear, therefore, that the diets of the negroes have a relatively high proportion of carbohydrate in the South where the incidence of diabetes is low, and that as they move north and come to take diets containing progressively smaller proportions of carbohydrate, the incidence of diabetes increases amongst them

TABLE V

Death rate from diabetes mellitus per 100,000 population in the States and cities of U S A in which classification into white and coloured is made The figures are the mean rate for 1920, 1925 and 1928 (42)

States	Death rate per 100,000		Cities	Death rate per 100 000	
	White	Coloured		White	Coloured
Alabama	7.8	7.0	Fort Worth	9.5	7.9
S Carolina	9.2	6.1	Dallas	14.2	15.8
N Carolina	8.7	7.4	Birmingham	15.2	9.8
Tennessee	7.4	8.4	Atlanta	13.1	14.2
Mississippi	10.1	6.3	New Orleans	19.5	19.9
Louisiana	10.7	7.8	Memphis	16.5	15.3
Florida	14.3	6.6	Nashville	15.3	16.0
Kentucky	9.0	12.4	Norfolk	13.0	9.5
Virginia	11.3	10.2	Richmond	18.2	12.8
Maryland	20.6	13.1			
<i>Average rate</i>	9.8	8.5	<i>Average rate</i>	14.9	13.4
			Washington	18.7	22.0
			Baltimore	25.4	17.3
			Louisville	20.0	16.8
			Indianapolis	21.8	15.6
			Kansas City Mo	19.0	22.3
			<i>Average rate</i>	21.2	19.0
			Mean rate for all above	17.1	15.4

It will be shown later that a very close relation exists between income and composition of the diet (Tables VIII and IX). It is an invariable rule that as income increases the proportion of carbohydrate in the diet falls, and if it can be assumed that the white working man in the Northern States is better paid than the white working man in the Southern then it can be deduced that the Northern white takes a diet containing a smaller proportion of carbohydrate than the Southern white. It has already appeared that in the case of the "coloured" American citizens increasing incidence of diabetes is found in association with the taking of diets containing a decreasing proportion of carbohydrate and an increasing proportion of fat. I would further suggest that if dietary studies are carried out in the different states on white persons of comparable social class, it will be found that the diabetic mortality of the whites is associated with a similar change in composition of the diet.

Dietary studies for Canada are not available. In Quebec, however, we have a population proud of its Latin ancestry, and if we can assume that their dietary bears traces of their origin it will be obvious that their preferences as regards food will be different from those of the contiguous American States. In 1910 Slosse and Waxweiler (55) found that the diets of Belgian workmen engaged in moderately hard work had an energy value of 3,972 calories and yielded 53% of calories from carbohydrate and 22.3% from fat. White workmen engaged in similar work in U.S.A. were found to take diets of 4,397 calories* containing 40% of carbohydrate and 37.7% of fat calories. In the absence of more definite information, however, I hesitate to suggest that the relatively low Canadian diabetic death rate is related to the difference between the diets of Northern States of U.S.A. and Canada.

Similar variations in diabetic death rates may be found in other countries. For example the rate in Scotland has always been lower than the rate in England. It is significant that from their experience of dietary surveys in both countries Cathcart and Murray remark "It is curious to note how definitely the fat content of the two English diets (families in Cardiff and Reading) is above that of any of these Scottish diets racial idiosyncrasy possibly plays a part. It certainly cannot wholly be ascribed to marked differences in income between the different communities" (9).

It may be concluded, therefore, that there is an association between the low death rate of rural communities, as compared with urban populations, and the typical rural diet which contains a smaller proportion of fat and a larger proportion of carbohydrate as compared with the diet chosen by a comparable social class in towns, although the calory value of the two diets is approximately the same. And it is probable that the progressively increasing diabetic mortality on proceeding northwards in the United States of America is also associated with a progressive diminution in the carbohydrate proportion of the diet.

Variations in the diabetic mortality rate of certain races in relation to change of dietary habits resulting from differences in environment

There appears to be unanimous agreement that the incidence of diabetes mellitus is very low in the lower social grades of coloured races resident in their native lands, but there is evidence that when these races are transplanted to westernised countries the diabetic mortality rate rapidly rises. The African negro provides a very good example of this change.

In Africa the incidence of diabetes amongst the negroes would appear to be extremely low. According to Mills (42), in two districts in Nigeria, where registration of the causes of death is compulsory, the diabetic

* Dunluce and Greenwood's calculation (12)

death rate among the natives in 1926 and 1927 was less than one per hundred thousand population. Ziemann (7) states that in the Cameroons it is very rare, Martin (35) confirmed its rarity on the West Coast of Africa in general, and Orr and Gilks (45) recorded no cases amongst 50,000 patients of the Kikuyu and 1,200 patients of the Masai tribe coming under treatment by the Kenya Medical Service. It may thus be concluded, even in the absence of reliable mortality figures, that diabetes mellitus is a rare disease amongst negroes in Africa.

Unfortunately I have been unable to discover any information regarding the diet of negroes resident in the old slave countries of West Africa, but reliable studies of East African native dietaries are available. The natives of Africa fall roughly into two groups—the pastoral tribes and the agricultural tribes. In a dietary study of two Kenya tribes Orr and Gilks (45) found that the agricultural Kikuyu tribe took diets containing 72.4% carbohydrate and 9.2% fat calories, whilst the nomad Masai tribe had a diet yielding 37.6% calories from protein, 12.4% from carbohydrate and 50% from fat. This latter diet contains the highest proportion of fat of any recorded diet but unfortunately the evidence as to the presence or absence of diabetes in this tribe is so scanty that no opinion can be expressed on the diabetic incidence rate. In Nairobi, Henderson and Kelly (19) gave the prison diet as containing 72% of carbohydrate calories and 14% from fat, and Donnison's (10) impression of the diet of East African natives in general agrees with these figures. It is probable that in the hot low-lying coast lands of the West where the ground is fertile and dense vegetation renders the country unsuitable for pastoral purposes, the diet of the natives approximates to that of the agricultural tribes of Kenya.

Turning now to the expatriated African negro in the United States it is found (Table V) that diabetes is not only a common disease but the diabetic death rate is equal to the rate in the white population of the same locality. As has been shown in the previous section, the diabetic death rate for negroes in USA increases at approximately the same rate as that for white persons as one proceeds northward. At the same time when negroes come north they rapidly adapt their dietary habits to those of the surrounding white people (52) whilst it is probable that in the south the dietary habits of the negroes are not far different from those of the southern whites.

The prison diets supplied in the south, as has been noted, contain about 60% of carbohydrate calories and 28% of fat calories. It is, therefore, a probable conclusion that the increasing diabetic mortality amongst negroes as one proceeds from Africa to the southern states of USA and from here to the more northerly states is associated with a change in dietary habits involving a gradual decrease in the proportion of dietary carbohydrate and a gradual increase in the proportion of fat.

A comparison of the Chinese in China and in U S A leads to the same conclusion Chun (10) reports that the Chinese diet in North China contains a large proportion of carbohydrate and a minimal proportion of fat He also reports that diabetes is rare amongst the natives of North China and in this observation he is supported by Mills (42) On the other hand, amongst the Chinese living in America, according to Joshn (28), the diabetic mortality rate is high Here again in the Chinese as in the case of negroes moving to the northern states, it is probable that a change in dietary, consequent upon the migration, has occurred

Two European races—the Irish and the Italian—provide interesting data The Irish emigrants come from the poorest sections of the agricultural community, and a dietary survey of 1911 shows that their diet yields 15.5% of calories from fat and 72% from carbohydrate (32) It is, therefore, of interest to note that the Irish Free State, which economically is the poorest section of the British Isles, has the lowest diabetic mortality rate In 1931 this was 8.2 as against 9.6 for Northern Ireland, 13.6 for Scotland and 14.5 for England and Wales The rates for the Irish in New York State are shown in Table VI It will be seen that even

TABLE VI.

Table showing the standardised diabetic death rates per 100,000 white persons in New York State of immigrants classified by country of birth (28)

Age groups	United States		England, Scotland and Wales		Ireland		Italy	
	M	F	M	F	M	F	M	F
All ages	15.4	16.1	15.1	18.8	18.4	28.7	4.1	8.0
25 — 64	21.1	21.6	10.5	20.3	30.8	46.2	9.4	14.1

in the year 1910, when the general rate for the U S A was much lower than in 1931, the death rate from diabetes amongst the Irish settlers in America was not only greater than in their native land, but even greater than amongst true born Americans Joshn (28) makes the suggestive remark that "the level of well-being and prosperity amongst the Irish in this country is far higher than in Ireland itself," and it is probable that coincidently with the increase in prosperity the diet has changed so as to contain less carbohydrate and more fat

The Italian immigrants to the United States form an interesting contrast to the Irish In 1910 the diabetic death rate in Italy was 4.7 and reference to Table VI will show that for the same year the Italian settlers in America showed a rate that was only a little higher than this It appears that Italian immigrants to the United States tend to form communities where their racial habits are to a considerable extent

preserved and a survey of the diets chosen in the Italian quarter shows that their dietary habits correspond closely to those of their countrymen in Italy (39) Typical Italian peasant diets in 1906 were found to yield 71% of calories from carbohydrate and 18% from fat (2)

It would be interesting to have data with regard to the dietary habits of Jews Joslin (28) has collected evidence showing that in Europe and in the old Jews of America the incidence of diabetes is very high He points out, however, that in his wide experience diabetes is no more common amongst young American Jews than amongst the rest of the population and the evidence of hereditary disposition is no stronger (26) It is, at least, possible in America where anti-semitic feeling is weaker than in Europe and consequently does not result in as strict segregation of the race, that the succeeding generations of American born Jews progressively acquire American habits and that after one or two generations their dietary preferences are those of Americans in general Unfortunately I have been unable to find figures relating to the food consumption of Jews in Europe so that it is impossible to tell whether American born Jews eat more carbohydrate than Jews brought up in Europe

Finally, a small but interesting point comes from India (7) Certain sects of the Hindus—the Jains and the Marwaris—are restricted by the tenets of their religion to a strictly vegetarian diet Hindus of other sects take a mixed diet The incidence of diabetes mellitus amongst the vegetarians is said to be low whilst amongst the less strict Hindus it is relatively high

It may now be concluded that when change in environment produces change in dietary habits, change in diabetic mortality is also found When the diet taken in the foreign land is found to contain a smaller proportion of carbohydrate and a larger proportion of fat than the diet of the native country, then the diabetic mortality in the new environment is higher than in the country of birth This association is independent of race and colour Where the diets of Europeans and Africans approximate then the respective diabetic death rates also approximate

The relationship of economic position and of occupation to the diabetic mortality rate and dietary habits of different social classes and different trades

The death rate from diabetes mellitus varies in different social classes A special report on this subject was issued by the Registrar-General (51) for England and Wales covering the years 1921 to 1923, and his results are shown in Table VII The data concern all occupied and retired civilians and these are divided into five social groups Class I the professions and the higher ranks of business life, Class II farm owners, retail merchants, clerks, teachers, etc, Class III skilled workers, Class IV semi-skilled workers including agricultural workers, Class V unskilled

workers In the last line of the table the figures for a similar report covering the years 1910 to 1912 (50), are given

TABLE VII

Table showing the rise in mortality rate from diabetes mellitus with social class in England and Wales (50) (51)

Age group	All occupied and retired civilian males	Social class				
		I	II	III	IV	V
1921-23						
All ages 20-65	12.2	15.2	17.7	11.2	9.2	8.1
16 - 19	3.3	2.6	2.3	3.8	3.2	2.8
20 - 24	4.5	4.3	5.1	4.5	4.5	4.2
25 - 34	5.5	6.3	7.1	5.3	4.7	5.2
35 - 44	6.7	4.7	8.0	6.6	6.6	5.2
45 - 54	12.8	19.0	19.3	11.5	8.9	10.7
55 - 64	32.4	46.8	55.1	30.4	21.4	14.5
65 - 69	65.3	153.0	114.3	61.2	36.2	26.5
70 -	99.7	203.9	177.2	71.7	56.4	45.7
1910-12						
All ages 20-65	10.0	14.0	14.0	9.0	4.0	8.0

It will be seen that as regards the death rate from diabetes at all ages the figures both for 1921-23 and 1910-12 show that mortality increases progressively with rise in social standing and economic position. An exception is seen in the 1921-23 figures in the higher rate of Class II than of Class I. This higher rate, however, disappears in the older age groups and the lead passes to Class I. It is possible that this finding may be reconciled with the results in general on the ground that economic eminence is seldom attained in the professions and higher ranks of business until middle age is reached. It should also be noted that the figures for the different classes refer to the years 1921-23 when insulin was first being introduced into medical practice, and it is to be presumed that insulin, at the price asked at that time, was more easily obtainable by members of the higher social and economic classes.

Dietary studies on the different social classes in Scotland have been carried out by Cathcart and Murray (9) and are shown in Table VIII. They found that the total intake of food was determined, not by the

severity of the manual work undertaken, but by the income received. As the income rises the calory value of the diet increases and the amount of protein increases in parallel so that the percentage of calories from protein remains remarkably constant in the different economic groups (Table VIII). The increase in calory value is brought about mainly by

TABLE VIII

Cathcart and Murray's (8) figures from a study of 105 families in St Andrew's, Scotland, 1930, showing that as income increases the proportion of carbohydrate in the diet falls and the proportion of fat rises

Average house keeping allowance per man fed (weekly)	Diet per man per day			
	Percentage calories			Calories
	from Carb	from Prot	from Fat	
8/6	58.2	11.3	30.5	2,341
12/3½	56.7	11.4	31.9	2,665
15/10½	55.0	10.6	34.4	3,240
18/3½	53.3	11.2	35.5	3,105
22/2½	51.8	11.0	37.2	3,244
30/2½	51.2	10.8	38.0	3,702

increased consumption of fat so that with rising income the proportion of fat in the diet rises and the proportion of carbohydrate falls (Table VIII). Similar results have been obtained by Pearl (48) in America.

This correlation between economic position and composition of the diet would appear to be a general rule for all races. Table IX gives a series of dietary studies in Bengal and the Indian United Provinces. It will be seen that the proportionate composition of the native diets varies in relation to social class in exactly the same way as it does in European diets, and it will be found on reference to the papers that here again with rising social class the calory value of the diet rises, the amount of protein increases in parallel and the amount of fat increases disproportionately. The general conclusion may thus be drawn that, with increase of income, diets of increasing calory value are taken and that these diets contain more fat and less carbohydrate. The bearing of this conclusion on the change in dietary habits of native races transplanted to countries in which the economic standard is higher, is obvious.

Figures with regard to the mortality from diabetes in India are fragmentary, but in two congresses held, one in 1907 (7) and the other in 1927 (13), there was unanimous agreement as to the incidence of diabetes in the different social classes. It was agreed that diabetes

mellitus is rare amongst the lower classes and extremely common amongst the relatively well-to-do. It is noteworthy that Dutt (13) emphasised the point that diabetes is common in just those social groups which take a relatively small proportion of carbohydrate in the dietary. The current belief that the relatively well-to-do Bengalis take a large proportion of their diet as carbohydrate is incorrect (Table IX). Fatty foods, such as ghee, are expensive and the poor cultivators cannot afford them, whilst the richer classes, following the general rule (Table VIII) take fatty foods in amounts which increase in proportion to their income.

TABLE IX

Figures showing the diets of different social classes in Bengal and the United Provinces (U P). The figures in parentheses refer to the publication from which the data were taken. The results show that the higher the social class the smaller the proportion of carbohydrate in the diet and the larger the proportion of fat.

Social class	Diet		
	Percentage calories		
	from Carb	from Prot	from Fat
Well to-do Bengali (38)	41.0	12.0	47.0
Well to do Bengali (4)	47.7	12.0	40.3
Professional men, U P (4)	48.2	11.5	39.3
Middle class (upper) Bengal (38)	52.0	12.0	35.0
Middle class (lower) Bengal (38)	71.0	9.0	20.0
Cultivator, U P (4)	77.1	13.1	9.8
Cultivator, Bengal (38)	81.0	8.0	10.0
Prisoner, U P (37)	82.0	12.0	6.0
Prisoner, Bengal (36)	81.0	9.4	9.6

In Egypt a similar correspondence is revealed (25). In this country also diabetes is common amongst the well-to-do and uncommon amongst the poor, and here again it is found that the poor take a large proportion of their diet as carbohydrate and a small proportion as fat.

It may be concluded, therefore, that with rise in social status there occurs an increase in mortality from diabetes and also a change in dietary habit so that more food is eaten and the constitution of the diet changed to contain a greater proportion of fat and a smaller proportion of carbohydrate.

DISCUSSION

Over-eating, excessive consumption of sugar and over indulgence in alcohol have all been indicted as significant factors in the aetiology of diabetes mellitus, and it is necessary first to examine the evidence upon which these general opinions are based

An association between the diabetic mortality rate and the total amount of food consumed is not suggested by the information I have been able to collect. It is true that in the section dealing with relationship of the increase in diabetic mortality to change in dietary habits consequent upon greater economic freedom, the total food consumption does increase as one proceeds up the social scale. But in the other sections no such parallel increase of food intake and diabetic mortality is found. From Table I it can be seen that there is no association between the diabetic death rate of the different countries and the calory value of the diet. A consideration of the English, Scottish and American dietary surveys for the last thirty years reveals no sign of an increase in food intake, although the diabetic death rate has risen steadily in each. During the war period in some countries the daily supply of food was certainly restricted but surveys carried out by Ferguson (16) during the years 1915 to 1917 on the same families show that, in Scotland, the daily intake of food only varied by about 200 calories during this period. Again the corrected rural diabetic death rate is consistently lower than the urban rate and yet the food consumption of comparable rural and urban economic groups is approximately the same. The evidence would therefore, appear to be against the suggestion that increased food consumption plays a significant part in determining the incidence of diabetes mellitus in different groups of people.

It is only natural that excessive consumption of sugar should sooner or later be suggested as a factor in the causation of diabetes mellitus. The work of Joslin, Dublin and Marks (28) and Mills (43) has, however, shown that there is no evidence in support of this suggestion.

The evidence with regard to the influence of alcohol on the national incidence of diabetes is small but definite. Ismail (25) stated that in Egypt diabetes mellitus was common amongst the well-to-do and rare amongst the poor, and he also pointed out that the majority of his patients had never touched alcohol in their lives. An inspection of the English figures (51), giving the mortality from diabetes mellitus in different trades, shows that the mortality amongst bar tenders is low and amongst brewers and maltsters only about the average for all occupied males. When it is remembered that in England it is still the custom for brewers to allow their employees a liberal quantity of free beer every day then, if alcohol favours the development of diabetes mellitus, it is surprising that the brewing trades do not figure high on the list of trades with

a high mortality from diabetes. It is probable, therefore, that alcohol plays no significant part in the causation of diabetes mellitus.

Of influences militating against the development of diabetes mellitus one only has been suggested. Bose (7) has suggested that hard manual work retards or prevents the progress of factors predisposing to the disease. This suggestion is in accord with clinical impressions and must be allowed as a definite possibility.

Joslin (26) has been so impressed by the association of over-weight and diabetes mellitus that he has said that diabetes is the penalty of obesity, and in a recent paper with Dublin and Marks (29) he has produced evidence which strongly supports this contention. The results of Himsworth and Marshall (22) obtained from a series of diabetics, of whom 60% were overweight, show that these diabetics, before the onset of diabetes, chose diets containing a diminished proportion of carbohydrate and an increased proportion of fat. The possibility suggests itself that the ingestion of this type of diet may be responsible for the obesity, in which case the more fundamental association of diabetes mellitus would be, not with overweight, but with the diet which, incidentally, promotes obesity.

The only dietary factor which can be correlated with the diabetic mortality rate is the proportionate composition of the diet. The information presented in this paper indicates clearly that a low death rate from diabetes is associated with a high percentage of carbohydrate in the diet, a high death rate with a low percentage of carbohydrate, and an increasing mortality rate with a diminishing percentage of dietary carbohydrate.

The significance of this association requires further discussion. Have potential diabetics an innate and possibly incidental preference for diets containing a relatively low proportion of carbohydrate and a relatively high proportion of fat? This suggestion appears untenable. It is impossible to imagine either that the innate dietary preferences of Irish immigrants change when they settle in America, or that the majority of Irish who migrate are predisposed to diabetes. It is also incredible that the high incidence of diabetes amongst the persons whose work brings them a high financial return, should be explicable on the grounds that ability to earn a large income is more prevalent amongst persons with a certain dietary tendency. And similarly the high diabetic mortality rate amongst white and coloured races in the northerly states of U.S.A. and the low mortality in the South, can hardly be explained on the grounds either that potential diabetics or persons with certain innate dietary preferences tend to congregate in different localities. The logical explanation of these examples, and of all the data that it has been possible to collect, is that the dietary habits of a people are determined by traditional or economic environmental pressure and that the diabetic death rate in a population is decided by the character of its diet. Change in the character of the diet so that it comes to contain a smaller proportion of carbohydrate and a larger

proportion of fat results in a rise in the incidence rate of diabetes mellitus

This conclusion is in agreement with the results of Himsworth and Marshall (22) They showed that diabetics prior to the onset of the disease took diets which, in comparison with the diets of non-diabetics, contained a lower proportion of calories from carbohydrate and a high proportion from fat The methods they used in their investigation did not permit them to draw conclusions regarding the difference in *amounts* of carbohydrate, protein, and fat ingested by the diabetic and normal group The data presented in the present paper, however, do permit a deduction to be made on this point

As has been pointed out the proportionate composition of the diet indicates national dietary preferences more surely than the absolute amounts of the different foods in the diet These latter are determined by the appetites of individuals whilst the proportions appear to be largely decided by the dietary fashion of the majority If now it can be shown that the average intake of food has remained approximately constant then change in the proportions of different foods in the diet necessarily implies change in the amounts of the different foods

In the last thirty years the calory value of the diet in England, Scotland and U S A has remained approximately the same, and as in these countries the national diet has progressively changed so as to contain smaller proportions of carbohydrate and larger proportions of fat, then the dietary change must have involved diminution in the amount of dietary carbohydrate and increase in the amount of dietary fat The equicaloric values of rural and urban diets and of Scottish families during the war reveal that the differences in proportion also involve differences in the amounts of carbohydrate and of fat It thus appears that ~~a rise~~ in the diabetic death rate is associated with ~~a diminution~~ in the amount of dietary carbohydrate and a rise in the amount of dietary fat

In a previous paper (21) I have shown that the sole dietary factor influencing the sugar tolerance and sensitivity to insulin of a healthy man is the absolute amount of carbohydrate in the diet Neither the calory value, nor the amount of protein, nor the amount of fat are of account in this respect The sugar tolerance and insulin sensitivity are high when large amounts of carbohydrate are taken and low when small amounts are ingested This result showed that more importance could be attached to variations in dietary carbohydrate than to variations in dietary fat and on the strength of this it was suggested (22) that the long-continued ingestion of a diet containing a relatively low amount of carbohydrate might eventually result in the permanent impairment of sugar tolerance and insulin sensitivity and finally produce diabetes mellitus It has been shown that the increase in diabetic mortality in the last thirty years has probably been associated with a steady diminution in the amount of dietary carbohydrate It is, therefore, possible that

the causative factor in the disease, diabetes mellitus, is not the low proportion but the insufficient amount of carbohydrate in the diet of the potential diabetics in the population

The lack of information regarding the caloric values of the diets of large groups of nationals renders it necessary to leave this as a possibility until such time as the necessary data are available. Then it will probably be found that the caloric value of the diet has varied so little that for the purpose of comparing national diets, proportion and amount of carbohydrate will have the same significance. The definite suggestion is now made that the proportion of carbohydrate in the diet is the determining factor in the development of diabetes mellitus.

It is now of interest to reconcile this suggestion with the other factors which are thought to influence the development of diabetes.

Susceptibility and hereditary predisposition (30) undoubtedly play a part in the ætiology of the disease, but, in my opinion, their rôle is confined to that of diathesis. The great rise in the diabetic mortality rates of different countries, during the last thirty years, is difficult to explain on the ground that a sudden widespread dissemination of hereditary susceptibility has occurred. A more logical explanation is that the susceptibility to the disease is widespread and that the increasing pressure of some external factor, which provokes the development of diabetes, is disclosing the frequency of this susceptibility. It is suggested that this external determining factor is that of diet, the ingestion of a low-carbohydrate high-fat diet. In any population there will be an unknown number of susceptible individuals and the susceptibility of these individuals will vary considerably. When the diet of the country contains a relatively large proportion of carbohydrate it will provoke diabetes only in those who are most susceptible and those who are less susceptible will not develop the disease. But if the diet changes so as to contain smaller proportions of carbohydrate, and correspondingly larger of fat, then the disease will be provoked in less susceptible subjects, and if the proportion of dietary carbohydrate becomes progressively smaller, individuals with slighter degrees of susceptibility will respond by developing diabetes. The incidence rate of diabetes mellitus in the population will thus rise in proportion as the diet changes. If this hypothesis is correct then it would be expected that the incidence of diabetes in different countries could be correlated with the proportion of carbohydrate in the national diet, that increase in the proportion of carbohydrate in the national diet would be associated with a fall in diabetic mortality, that variation in the proportion of dietary carbohydrate consequent upon change in environment would produce change in the incidence of the disease, and that variation in the proportion of carbohydrate in the diet of different classes and in different parts of one country would be reflected in changes in the diabetes

incidence rate The information presented in this paper fulfils these expectations

It would thus appear that the most efficient way to reduce the incidence of diabetes mellitus amongst individuals predisposed to develop this disease would be to encourage the consumption of a diet rich in carbohydrate and to discourage them from satisfying their appetite with other types of food

SUMMARY

1 Data are presented showing the different diets eaten by different races, nations and social classes throughout the world and a correlation has been demonstrated between dietary preference and the incidence of diabetes mellitus. The incidence rate of diabetes mellitus has been assumed to be reflected by the mortality rate

2 It is shown that —

- (a) countries in which the incidence of diabetes mellitus is high are countries in which diets containing a relatively low proportion of carbohydrate and high proportion of fat are chosen, whilst those in which the incidence is low take diets with a high proportion of carbohydrate and low proportion of fat,
- (b) the rise in the incidence of diabetes mellitus which has occurred in the countries of the Western civilisations during the last thirty years has occurred concurrently with a change in dietary preference by which a progressively greater proportion of fat and smaller proportion of carbohydrate has been chosen. The proportion of protein and the calory value of the diet have remained unaltered,
- (c) the fall in diabetes mortality that occurred during the World War is shown to be related to restriction of food supplied. This restriction involved reduction in the proportion of fat and increase in the proportion of carbohydrate. Reduction in caloric intake was slight in most countries but marked in Germany,
- (d) the incidence of diabetes is higher in urban than rural population. Urban diets contain a smaller proportion of carbohydrate and greater proportion of fat than rural,
- (e) the incidence rate of diabetes rises steadily from the southern to the northern states of USA and then drops sharply as the Canadian border is crossed. Evidence is brought forward that the proportion of fat in the diet changes in parallel with the diabetic incidence rate,

- (f) race is not a factor in the incidence rate of diabetes mellitus Transplanted races manifest the same incidence rate as prevails in the surrounding races of the new country Data are produced which indicate that migration brings about change in dietary habits so that immigrants gradually acquire the dietetic preferences prevalent in the new land Rise in the diabetic incidence rate always appears to ensue if the proportion of carbohydrate in the acquired diet is smaller and the proportion of fat is greater than in the diet of the native land ,
- (g) with rise of economic position there is a corresponding rise in the diabetic incidence rate and at the same time a change in dietary habits so that a smaller proportion of carbohydrate and a greater proportion of fat are taken

3 The available data do not suggest that excessive consumption of sugar and over indulgence in alcohol play a part in the aetiology of diabetes mellitus The data with regard to the total quantity of food eaten show that there is no definite correlation between rise in the incidence of diabetes and over-eating It is suggested that prediabetic obesity is an effect of the type of diet eaten

4 A close correlation exists between the incidence of diabetes mellitus in different races, nations and social classes and the proportionate composition of the diet A high proportion of carbohydrate and low proportion of fat is found in all cases to be associated with low diabetic incidence , whilst a low proportion of carbohydrate and a high proportion of fat are associated with a high incidence

5 The available information suggests that the different diets chosen vary little in calory value If this is correct then the same correlation which exists between the incidence of diabetes and the proportionate composition of the diet also holds between the incidence rate and the absolute amount of carbohydrate or of fat in the diet In this case it can be said that the incidence of diabetes is high where relatively low-carbohydrate diets are taken, and that the incidence is low where relatively high-carbohydrate diets are chosen

6 In view of previous results which show that a low-carbohydrate diet results in an approximation of the metabolic findings in a healthy individual to those found in the diabetic, it is suggested that the ingestion of a relatively low-carbohydrate diet is the factor determining the onset of diabetes mellitus in individuals with a predisposition to the disease, and that if a high-carbohydrate diet had been taken a considerable proportion of these individuals would not have developed diabetes

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CIRCULATORY CHANGES IN THE FINGERS IN SOME DISEASES OF THE NERVOUS SYSTEM, WITH SPECIAL REFERENCE TO THE DIGITAL ATROPHY OF PERIPHERAL NERVE LESIONS

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THE original object of our observations was to determine the mechanism of the vascular and nutritional changes that occur in the fingers when their nerve supply is divided. In the course of this work it became necessary to become familiar with the effects of simple disuse, of lesions of the motor nerves, and of sympathetic lesions, for the effects of these relatively simple disturbances help us to analyse the more complex effects of mixed nerve section. Had it been possible to study also the effects of degenerative lesions of pure sensory nerves, the analysis might have been carried more securely to completion, but this evidence is very rarely available in man except in the instance of the 5th cranial nerve.

We found that effects of disuse can be identified, that different and recognisable vascular effects follow loss of motor, sensory, and sympathetic innervation, and that nutritional changes follow in different degrees upon these disturbances. Thus, as the investigation proceeded (and included, not only peripheral, but some central nervous diseases) it became more and more apparent that most if not all those changes included under the term "vasomotor disturbances" are capable of simple explanation, and that many of the changes commonly described as "trophic" are merely the effects of disuse, or are nutritional changes due to altered blood supply. Although many of the related problems still remain for solution, and our present conclusions sometimes lack finality, our investigation has gone far enough to make it clear that persistent research is all that is required quickly to solve the problems in question and to make the changes in the skin and underlying tissues in nerve lesions clearly understandable.

Throughout our work, vascular disturbances in the limbs have claimed particular attention. In studying the state of the circulation through the limbs we have used chiefly the skin temperature. And since a main object has been to ascertain any abnormalities of the circulation in the circumstances

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ordinarily ruling in the patient's life, the skin temperatures have been measured after exposing the limbs symmetrically for 15 minutes or more in the laboratory, the patient having previously come from the ward or out of doors. In each patient we satisfied ourselves that any differences in temperature observed between the two symmetrical limbs were usual in these circumstances, and that such differences were not due to previous unequal exposure or unequal direct heating. In most of those cases showing unequal skin temperatures on the two sides we also subjected the limbs to more detailed tests in order to throw light on the cause of the inequality. These tests will be described briefly when necessary.

These investigations, requiring numerous repetitions of simple and special observations on each case, have been carried out upon many cases belonging to a number of categories of disease. To include a full description of individual cases studied, or of observations made, would make this paper too long, we therefore confine ourselves to illustration and to general statements.

The effects of simple disuse

Long continued immobility The effects of long continued immobility without change in the nervous system, are illustrated by the three following cases.

Case 1 J M, a man of 40 years, had crushed his left 3rd and 4th fingers, the wounds become septic and healed slowly in a month. For three months the movements of the hand and particularly of the two named fingers had been very limited. The affected fingers showed the scars of injury, were a little deeper and bluer in colour and showed fewer and shallower transverse furrows and small wrinkles than did the other fingers, otherwise the skin and nails appeared similar in the two hands. There was no atrophy. The 3rd and 4th fingers and to a less extent the other fingers of the left hand were usually colder than those of the right, but in a warm room all the fingers would warm to the same high point.

Case 2 P T, a man of 38 years, had been hit by a bullet 12 years previously, an injury which was accompanied by damage to the tendons on the dorsum of the left hand, and was followed by necrosis of metacarpals and fixation of joints. During the 12 years there had been little or no movement of any finger, except a little flexion of the terminal joints, and the hand was in consequence little used. The 2nd to 5th fingers were a little narrower throughout their length on the left hand, the pad of the 2nd left finger was definitely atrophic (Fig 12), but the pads of the remainder were normal. There was less furrowing of the dorsal surface of the left as compared with the right fingers, as is usual in disuse, consequently the skin of the left was smoother than that of the right fingers. The nail of the 2nd left finger was a little narrowed and increased in convexity, the others were quite normal. The texture of the skin was little changed. Although often colder than the right when exposed in winter time, the left hand warmed quickly

in warm rooms and there was ordinarily little difference in the temperature of the two hands

Case 3 T, a pathologist, had acquired an infection of the palm of the right hand and base of the index finger 5 years previously, the tendons of the finger became involved and the interphalangeal joints quite fixed in a semiflexed position. The nerves of the finger were undamaged. The finger was little used except for writing. The subject found this finger constantly colder than the others on cold days, and he had noticed indolent healing of small lesions of the corresponding knuckle. The soft tissues of the finger were atrophic in its whole length, atrophy of the pad being pronounced and the nail increased in convexity. The skin of the dorsal surface was less wrinkled, and therefore a little more shiny, smoother, and seemingly thinner and less mobile, than that of the other fingers.

These cases are described to show how simple disuse of one or more fingers leads to definite changes in them. Immobility leads to lowered temperature with which is associated increased vascular colouration of the skin, it leads also to loss of furrowing and gives to the skin a smoother surface, a change which, as the first case shows, becomes evident within a few months. But the more profound changes, which develop only after long disuse, are atrophy of the soft tissues and particularly of the pulp of the fingers, accompanied by narrowing and increased curvature of the nails. Occasionally, as in the third case, indolent healing following injury occurs. It has long been recognised that similar changes occur in the extremities in diseases of the central and peripheral nervous system and examples will be described in the course of this paper. Occurring as a consequence of a nervous lesion these changes have been attributed to the disturbance of some trophic function exercised directly through the nerves, in the cases just described the nervous system was intact and the changes in the digits must be attributed directly or indirectly to disuse. The following cases illustrate the effects of disuse consequent on a functional or organic lesion of the central nervous system.

Hysterical monoplegia W H, a man of 39 years, had suffered from complete hysterical paralysis of his right elbow, wrist, and fingers of 23 months' duration, for the first 15 months the arm was splinted, for the last 8 months treated by massage and electrical stimulation. The right arm was completely insensitive below a transverse line about 3 inches above the elbow. In the very last few days he had begun to show recovery of voluntary movement, feeble adduction of the right thumb being possible.

The right hand was flaccid, its fingers being a little over-extended, the fingers could be flexed passively by no more than 45° at any joint. The right index finger and thumb showed slight but distinct tapering and the other fingers of the right were just discernibly smaller than those of the left hand. The nails of the first and second fingers were distinctly, and the rest very slightly, narrowed. An increase in lateral curvature of the nails was definite in all, but especially in the first two nails, which also showed

distinct longitudinal overcurvature The pads of the right fingers were normal in general outline, but very soft, and furrowed longitudinally, an appearance suggesting atrophy of subcutaneous tissue without corresponding tightening up of the skin The skin over the fingers was everywhere at least normally mobile and easily thrown into folds But apart from the pads of the fingers, the natural folds and ridges of the skin were much diminished on the right side, thus the ridges and furrows on the extensor surfaces of the joints were almost lost and the minute natural ridges of the palmar surface reduced, the skin appeared smoother than normal The hairs were long on the paralysed hand, but broken off short on the normal hand

The affected hand was conspicuously paler than the normal one, the pallor being chiefly due to emptiness of the minute blood vessels, but in part to deficient pigmentation of the skin, the palmar surface showed unusual mottling of pink and white areas During several weeks' stay in hospital the hands had often been noted to be equal in temperature, but from time to time the affected hand was the cooler, when the patient walked out on cool days, both hands being allowed to swing by his sides, the paralysed hand and arm was observed soon to become definitely colder than the unparalysed one, a fact of which the patient himself was fully aware

The effects of disuse resulting from hysterical paralysis which this case illustrates have been fully described by Hurst (10) who has shown that if the paralysis is cured by psychotherapy, the nutritional changes in the digits quickly disappear, convincing evidence that the changes result from disuse

Hemiplegia The effects of disuse resulting from a cerebral lesion are illustrated by the following case

Mrs E B, aged 55 years, suffering from mitral stenosis and auricular fibrillation, was examined 3 months after the sudden onset of paralysis of the left side of the face, the left arm, and leg The left upper extremity was spastic and partially flexed at elbow, wrist, and fingers, slight flexion of the elbow and fingers being the only voluntary movements The muscles of the left forearm and hand were slightly smaller than the right, sensation was normal The left hand was a little swollen, and the skin shiny, with loss of its wrinkles There was no atrophy of the fingers The left forearm and hand were a little deeper in colour than the right The affected hand was usually warm and on several occasions was found to be warmer than its fellow when both were at rest and exposed equally in cool atmospheres, when the body temperature was raised the fingers of both hands warmed to temperatures similar to those shown by normal fingers in such circumstances Six months after the onset, the paralysis and posture of the arm were unchanged The skin over the backs of the left digits, and to a less extent the back of the left hand, was smooth from loss of wrinkles both over and between the joints The pulp of the fingers was slightly atrophied and softer on the left side, and the nail of the index finger increased in lateral and longitudinal

curvature Nail growth was slightly slower on the affected as compared with the unaffected side When exposed equally the hands were usually equally warm, though occasionally the affected hand was the cooler Eighteen months after the onset, the condition was unchanged

The most remarkable feature of this patient was the greater warmth of the affected limb at the 3rd month, in spite of its complete disuse It should be said that this patient was in bed when these observations were made, the comparison was therefore between a spastic completely disused limb, and a normal but little used limb Our experience is too limited for us to state whether the tendency for the paralysed limb to be the warmer in the early stages of hemiplegia is or is not the rule In two patients who were seen three years after the onset of a complete spastic paralysis of one upper and partial paralysis of the corresponding lower limb resulting from a cerebral vascular lesion, the paralysed limb was ordinarily cooler than the normal limb, both these patients presented atrophic changes in the digits similar to those in the patient more fully described, in one in whom the test was made a normal vasodilator response to warming the body was shown by the paralysed fingers Both these patients were walking about and the comparison was between a completely disused spastic limb, and a fully used normal limb

Effects of motor nerve lesions

Progressive muscular atrophy Two men, aged 39 and 48, suffering from progressive muscular atrophy, of 16 and 2 months duration respectively, were investigated In each case the atrophy was advanced in one upper limb, affecting particularly the small muscles of the hand and to a less extent the muscles of the forearm, while the other upper limb was little changed Opportunities were thus provided for comparing normal and abnormal hand Neither of these patients omitted to use the affected hand, both were receiving treatment by massage while under observation In neither were there any differences between normal and abnormal hand in the texture of the skin or nails, or in the rate of growth of the latter in the first case, in which it was measured, the fingers showed no atrophy There was, however, in both cases a definite tendency for the affected hand to be cooler than its fellow Thus when the hands were exposed in cool rooms (15° to 17°C) it was the rule for the skin temperature of the fingers and hand to be several or many degrees less on the affected than on the unaffected side, prolonged voluntary movements of the fingers of both hands had little effect in equalising temperature In colder rooms the hands would become equally cold If both hands were immersed in water at 38° for 10 or 15 minutes and then laid at rest in a room at 15° to 17° , a difference in temperature soon became established between them, the affected one becoming distinctly the cooler (Fig 1) Although the hands usually presented the difference of temperature described, directly warming the trunk caused the temperature of the two hands to rise to the same high level on both

sides (Fig 2) The rise of temperature in the affected hand was delayed, though the difference in the time of warming was no greater than that found between two normal hands in which a similar difference of temperature

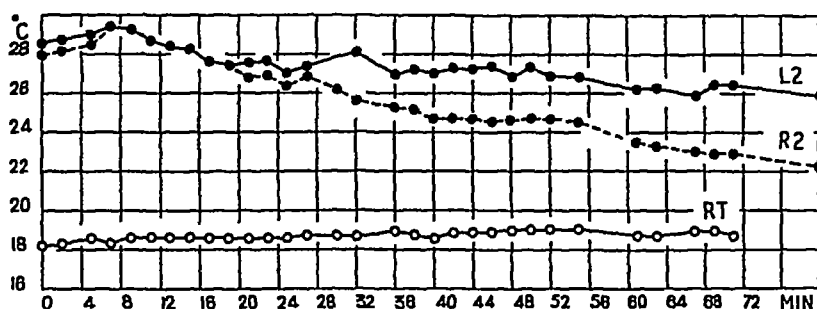


Fig 1 K, aged 30, suffering from progressive muscular atrophy affecting the right hand almost exclusively The observation was made 6 months after the onset of the disease Both hands were immersed in a bath at 38° for 15 min, taken out, and dried The charted temperatures were taken from the left (L2) and right index (R2) fingers by means of thermoelectric junctions fixed just proximal to the nails R T = room temperature, taken by a junction in the air near the hands The chart illustrates the quicker cooling of the fingers of the right hand

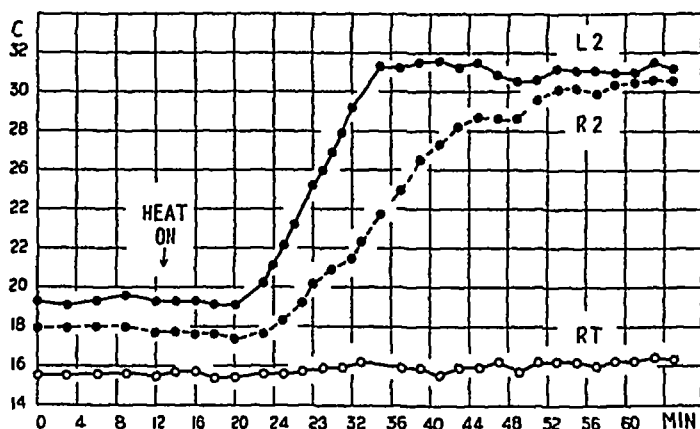


Fig 2 S, a man of 48 years, had suffered from progressive muscular atrophy, affecting the right hand especially, for 2 months The charted temperatures illustrate the behaviour of the fingers in a cold room The fingers of both hands were at first cold At the arrow, while the hands still rested on a table, the trunk was enclosed in a chamber, the temperature of which was raised gradually to 47° General vasodilatation occurred, which involved both hands, the right one after a few minutes delay Temperature from the two index fingers, just proximal to their nails, and from the air near the hands (R T)

has been established by preliminary soaking in baths at different temperatures (16) Numerous observations with Stewart's calorimeters (standing at about 32°C) showed the heat elimination by the affected hand to be much reduced in cool rooms (17°C), but in warmer rooms (21°C) the first patient

continued to show the difference while the second presented none. Colour differences noted in the two hands were inconspicuous and not more than those seen in normal subjects whose hands are made by immersion unequal in temperature to a similar degree.

Anterior poliomyelitis. Two girls of 21 and 8 years had suffered for 10 and 6 years from the effects of anterior poliomyelitis, which had led in both cases to severe atrophy of the muscles of the left lower limb and particularly of those below the knee. Both patients suffered in the winter time from chilblains confined in the one and almost confined in the other to the paralysed foot, these would start as itching red swellings, which would often break down and continue as indolent ulcers while the cold weather lasted. The state of these limbs, subject to long continued disuse during

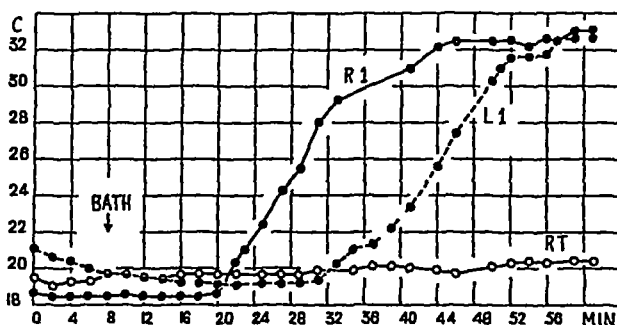


Fig 3 R 8, a girl aged 8 suffering from anterior poliomyelitis of the left leg of 20 months duration. The chart is of the temperature of the first toes of the right and left foot and of the air near these toes. After exposure in the cool room the feet were almost equally cold. At the arrow, the left arm was immersed in water kept at 43.5° for the period covered by the rest of the chart. General vasodilatation followed, in which both feet were involved. The response of the left foot lagged behind that of the right.

the growing period, was carefully investigated and may be described briefly. In both patients, and particularly in the younger, the whole limb and foot was shortened, the toes were smaller and their bones less dense to X-ray penetration on the affected side. In both the colour from the knee down was deeper and ordinarily more cyanotic in the affected than in the normal limb, the discoloration of the foot was conspicuous. In addition to the general discoloration there were patches of deeper colour on the foot of both patients, these patches were left by the healing chilblains or ulcers. In the older patient, whose affected foot was often perceptibly swollen after it had been hanging down, the little transverse wrinkles of the skin were less in evidence, and the skin as a consequence was a little smoother than that of the affected foot. Otherwise the texture of the skin of the foot over the greater part of its extent was very little changed in either patient. In the younger patient the affected leg was less hairy than its fellow. In both patients and in warm rooms the affected was nearly always colder than

the unaffected limb, especially at its extremity where the difference of temperature amounted to several degrees. Warming the body by immersing one or both arms in hot water caused the temperature of the toes to rise to the same high level on the two sides (Fig 3). When fully warmed by this means the pulsations of the arteries of the feet were palpable and equal on the two sides in both patients, and the skin of the toes exhibited very distinct capillary pulsation. Thus the vessels of the feet were shown to be normal and capable of good expansion.

These patients with anterior poliomyelitis are peculiar, amongst the material we have examined, in showing a considerably diminished size as well as a diminished density of the bones of the paralysed limb, a feature no doubt to be associated with the occurrence of paralysis during the growing period. The extent to which the deficient bone growth is to be attributed to the muscular paralysis and wasting or to the associated decline of bloodflow may become evident when the ultimate effects of early sympathectomy have been carefully investigated.

The mechanism of vascular and digital changes in disuse

The vascular disturbance has been found to be of the same kind in all these cases of chronic immobility of a limb whether this results from muscular paralysis or from fixation of joints or tendons. In ordinary circumstances the bloodflow to the affected limb is reduced, as displayed by relative coldness of the skin, or by this and by the reduction of its heat elimination, as shown when the limbs are immersed in calorimeters. If, however, the body of such a patient is warmed, the vessels of the affected limb dilate fully and the skin of the limb attains a temperature as high as that on the normal side. The reduction in bloodflow is thus discontinuous, for it disappears when vasomotor tone is relaxed. It is evident that, since in these patients the vessels are capable of good expansion, the reduction in bloodflow to the paralysed limb is not due to obliterative vascular disease but to increased arteriolar tone. The integrity of the vasomotor nerves to the limbs in these cases is demonstrated by the normal vasodilator responses to raising body temperature, the difference in the times of onset of the responses in disused and normal limb being no greater than may be seen in symmetrical normal limbs previously rendered unequal in temperature to a similar degree by immersion in baths at suitable temperatures.

This reduced bloodflow does not require prolonged disuse for its development, the change follows almost immediately the hand ceases to be used as can readily be observed in healthy people. If a normal subject moves in a room at about 16°, one hand being used for work such as note taking, moving books and so forth, the other hand being kept still and hanging by the side, the unused hand becomes definitely cooler (for example 3° or 4°C) than its fellow in about half an hour. It seems unlikely that the greater warmth of the used limb can be accounted for by the facilitation of venous return by the working muscles, though this may contribute. If

a hand is placed palm downwards on a table and voluntary movements of the hypothenar muscles are maintained continuously, the ulnar side of the hand becomes hotter relative to the radial by as much as 2° to 3°C within 10 minutes (at room temperature of 16° to 18°C), this increase in the temperature of the ulnar side of the hand may be accompanied by a distinct though less conspicuous warming of the 5th as compared with the 2nd finger, presumably because the corresponding digital vessels are dilated in the early part of their courses by the greater temperature of that part of the hand through which they pass. It is suggested that the increased bloodflow through the skin of an active limb is largely due to the direct dilator action of the raised temperature of the active muscles on the neighbouring vessels, but we are doubtful if this explanation accounts for all the phenomena observed. In this connection it is of interest to note that the hemiplegic patient was exceptional in that the paralysed hand was ordinarily warmer than the resting normal hand in the early stages of the disorder, it may be suggested that this exceptional state was due to the increased tone and resultant increased bloodflow through the muscles of the spastic limb. Again, it has been shown by calorimetry and curves of cooling that when patients with progressive muscular atrophy are exposed to cool atmospheres, the bloodflow through the fingers and hand on the affected side is less than on the normal side, although both hands are at rest. This difference, which disappears when vasomotor tone is relaxed, is probably a consequence of a diminished bloodflow through the atrophied muscles.

Our observations leave little doubt that the bloodflow through the skin of the limb depends much on the state of its muscles, but whether these variations in cutaneous bloodflow are determined entirely by temperature changes arising directly out of muscular activity, or whether there is some additional mechanism for increasing the blood supply to the limb as a whole, remains undecided.

It has been seen that two possible causative factors are common to the various types of case presenting atrophic changes in the digits and already described, namely, disuse itself and a reduction in bloodflow, in all these types the reduction in bloodflow is discontinuous, the vessels opening fully when the body is sufficiently warm. In most of the cases disuse and reduced bloodflow are so closely associated that it is impossible to say which is the more responsible for the atrophic changes. In two cases a judgment can be given. Thus in the patient with progressive muscular atrophy, observed till the 16th month of the disease, there were no changes in the skin or nails of the affected hand, which was used by the patient for all his ordinary light occupations such as eating, dressing, and smoking, nevertheless the reduction in bloodflow to the affected hand was conspicuous from the 4th month onwards. In the patient with hemiplegia the fingers showed distinct atrophic changes by the 6th month, and the affected limb was completely disused but failed to show any definite reduction in its bloodflow. The first of these two cases shows that in the absence of disuse, a reduction

in bloodflow of the intermittent kind here described may be unaccompanied by atrophic changes. The second case shows that complete disuse even without an associated decline in bloodflow may lead to atrophy of the soft tissues and particularly of the pulp of the fingers with increased lateral and longitudinal curvature of the nails. In cases of the types already described it thus seems probable that disuse itself is the more important factor in producing atrophic changes, but it is to be emphasised that in them the reduction in bloodflow is discontinuous and often inconsiderable. It will be shown later in this paper that a reduction in bloodflow that is both persistent and considerable may lead to atrophic changes even in the absence of disuse.

Effects of loss of sympathetic supply

The following account of the effects of sympathectomy is based on a study of patients from whom cervical or lumbar ganglia have been removed and in whom the corresponding limbs were free or relatively free from vascular disease. Some of these studies have been already published (14).

The temperature of a limb within a few hours of dividing its sympathetic nerve supply is that of its fellow in full vasodilatation. A state of full vasodilatation after sympathectomy is, however, only temporary, after several days have passed the temperature of the sympathectomised limb is a few degrees less than that of its fellow from which vasomotor tone has been released by warming the body. Thus it is not strictly true to say that a sympathectomised limb is hotter than a normal limb, it is only when vasomotor tone is such that the vessels of a normal limb tend to close down under its influence, as when the body is cool or warm but not hot, that the sympathectomised limb is the hotter. The vessels on the affected side respond little if at all to changes in body temperature, and thus the affected limb maintains a very uniform temperature, above and below which the temperature of the normal limb swings in response to changes of vasomotor tone (see Fig. 4). The stability of tone in the vessels in the sympathectomised limb is conspicuous, and the tone is itself appreciable or considerable.

The return of vascular tone after sympathectomy is known to affect the minute vessels, giving rise to pallor, and probably to affect also the arterioles, which would more importantly reduce blood supply. The nature of the factor increasing tone remains obscure and has been fully discussed elsewhere (14) and recently by Grant (4), it is sufficient to remark here that in man the vessels of the sympathectomised limb respond more vigorously to constrictor agents such as adrenaline (2, 4) and to dilator agents such as histamine (14).

In a number of sympathectomised cases, of recent and old standing, search has been made for changes in the skin other than vascular. The skin is dry owing to the usual absence of sweating and in one case a little fine flaking of the skin could be attributed to this cause. Otherwise, no change in texture has been noticed, the nails remain well formed and in the

one case in which rate of growth was measured it remained the same as on the normal side

Effects of motor and sympathetic nerve lesions combined

In the two cases already described of paralysis of the left leg due to anterior poliomyelitis, a left lumbar sympathectomy was eventually performed. This operation was done in each case with the idea of improving

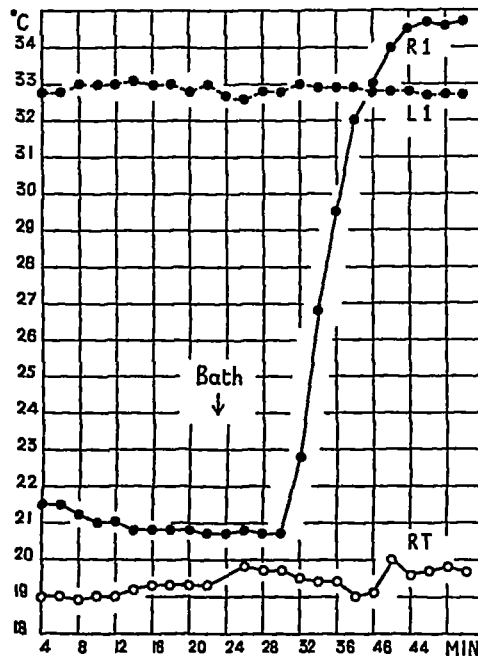


Fig 4 C.H., aged 21 anterior poliomyelitis of left leg of 11 years duration. Left abdominal sympathectomy on April the 7th. The chart is from an observation on April the 25th. In a room at 19° the right toes were 11° colder than the left toes. At the arrow, both arms were placed in water at 43° until the end of the observation. The right foot, but not the left responded in the general vasodilatation.

the condition of the ulcerated skin. The effects were the same in the two patients. The bloodflow to the limb greatly improved, whereas the foot before operation was colder, it now became in ordinary circumstances warmer than its fellow and this state persisted for months of observation. The depth of skin colour decreased, cyanosis was abolished, and the indolent ulcers healed. The healing of ulcers and protection against further ulceration is now a recognised result of this treatment of such cases, (see Gask and Ross (3)).

The cases of combined motor and sympathetic lesions here briefly described become important when compared with cases of transection of

mixed peripheral nerves, in these a lesion of sensory nerve fibres is added and the effects of this addition are displayed.

Effects of mixed peripheral nerve section

The following account of the results of peripheral nerve section is based on a study of four cases of complete section of the median nerve,

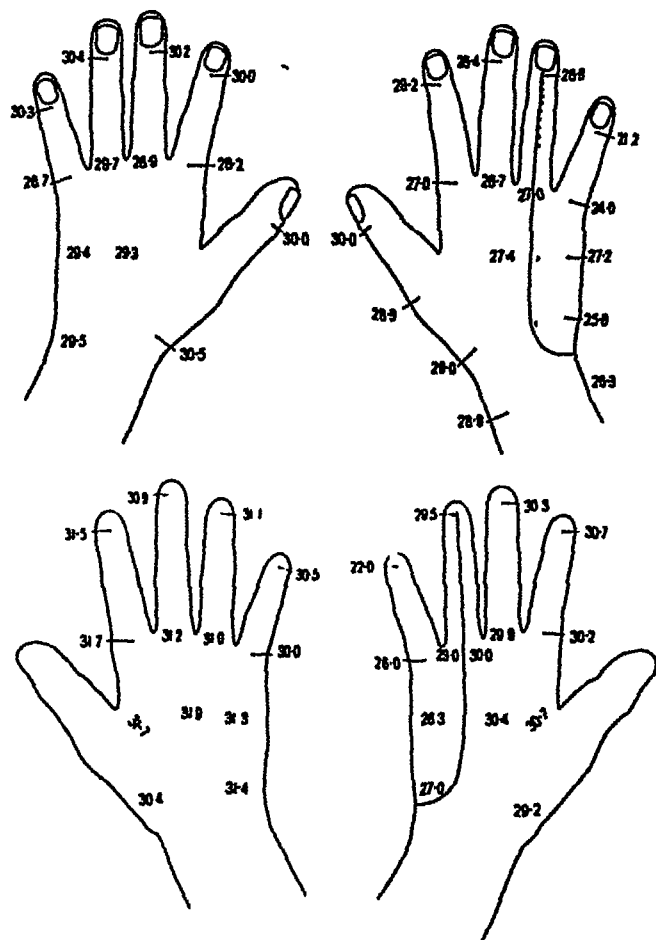


Fig 5 L.B, severed his right ulnar nerve on July the 14th, 1931 The figure shows the area of anesthesia (solid line) and analgesia (broken line) on August the 13th, and illustrates the relative coldness of the right ulnar region when compared with the rest of the hand The temperature value is either written directly over the point tested, or the position of the latter is indicated by a pointing line The temperatures of the left hand were taken simultaneously as a control The patient was resting with the hands on a cork table, the temperature of the air near the hands was 20.4°

and one of degeneration of the median nerve following its injury from a fracture of the humerus involving the elbow joint, of five cases of section of the ulnar nerve of which three were proximal to the elbow, and of one case

of injury to the ulnar nerve in a fracture involving the elbow joint. Cases of section of the ulnar nerve distal to its dorsal branch have been excluded, because denervation of the affected fingers is incomplete. The earliest case seen was two days after section, the latest 14 years. In many instances of nerve section, other important structures such as tendons and arteries

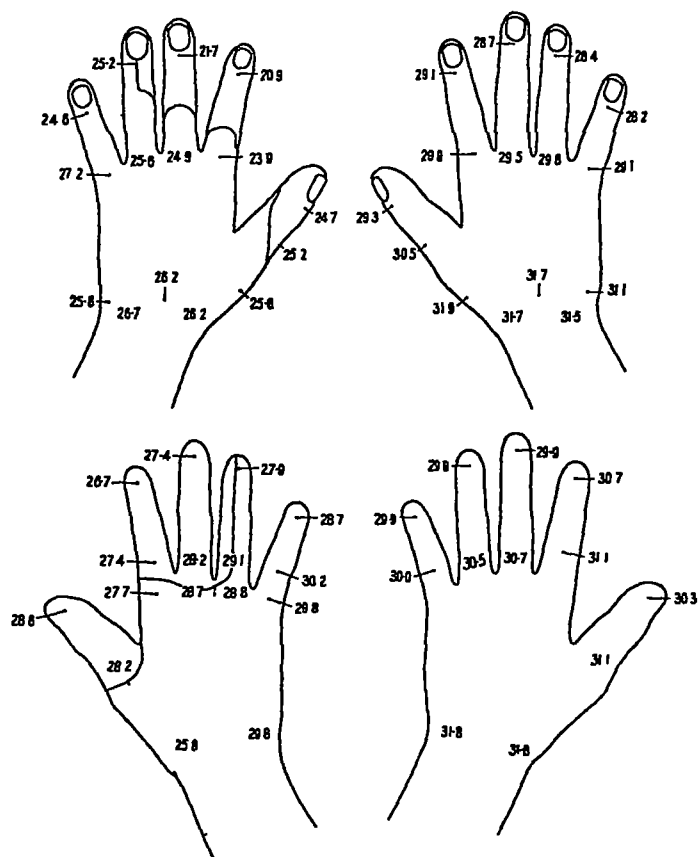


Fig. 6 J W, aged 31, severed his left median nerve on April the 17th, 1929. The figure shows the area of complete anaesthesia and analgesia (solid line) and incomplete loss of sensation (broken line) on October the 25th, 1930, and illustrates what was a usual and persistent difference of temperature between the left median and ulnar areas. Readings from the dorsal surfaces of the hands and from their palmar surfaces were not taken at the same time, and consequently are not strictly comparable. The patient was at rest in a room at 17.5°.

may be injured, in many a contracture of the fingers develops with fixation at the joints. The digital and vascular changes which we shall describe occur in patients in whom the nerve is the only important structure injured and in whom the joints of the affected fingers can be freely moved passively.

Decreased bloodflow. Section of a mixed nerve trunk supplying the fingers leads ultimately to diminished bloodflow to the corresponding area

as is shown by coldness of the skin. The coldness is persistent. Naturally there are periods when the hands and body are chilled and when the temperature of the extremities falls to that of the atmosphere, there are other periods, for instance while the subject is in bed, when the hands are directly warmed, in these circumstances the temperatures on normal and abnormal side may differ little. But apart from these unusual circumstances the anæsthetic skin is persistently colder and often much colder than the normal skin. If the hands are thoroughly warmed by immersing them in a bath at 35° for 15 minutes and then exposed in a cool room (16° to 18°C), the temperature of the anæsthetic fingers falls more rapidly than does that of the unaffected fingers and a considerable difference of temperature soon becomes manifest. An illustration showing the close correspondence between the area of anæsthesia and that of coldness in our patient K R, 8 months after section of the ulnar nerve, has been given in an earlier paper

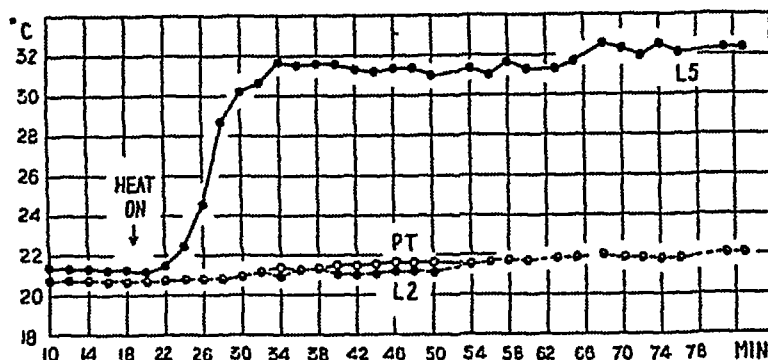


Fig 7 W L, a man of 19 years, had severed his left median nerve at the wrist on April the 2nd, 1931. It had been resutured. A chart of the temperature of the 2nd and 5th fingers of the affected hand on July the 7th, 1931. At the arrow the trunk was enclosed in a chamber the temperature of which was gradually raised from 35° to 63° . In the general vasodilatation, which soon followed, the temperature of the unaffected finger (L5) rose fully, while the anæsthetic finger (L2) remained at that of the surrounding air. At the time, atrophic changes in fingers L 1 and 2 were already distinct, the bones were just beginning to show rare action. The 2nd left finger showed no flare to histamine, nor rise of temperature during exposure to ice cold water.

(12), a similar illustration is shown in Fig 5 from L B 2 months after ulnar nerve section. Fig 6 shows the areas of anæsthesia and coldness in J W $1\frac{1}{2}$ years after section of the median nerve. It will be seen from these illustrations that not only is anæsthetic skin colder than sensitive skin, but that the sensitive skin on the side of injury tends to be a little cooler than the corresponding skin on the other side. This may be attributed partly to relative disuse of the hand as a whole, possibly it is partly due to loss of heat to the adjoining cold and anæsthetic parts and to the cooling effect of blood returning through the veins of anæsthetic fingers to the palm, there to diminish the flow through the palmar arteries. To the temperature

of the returning venous blood may also be attributed the occasional extension of the area of relative coldness of the ulnar side of the limb well beyond the upper margin of ulnar anaesthesia, as is shown for example by the value (26.3°) of the proximal dorsal reading in Fig 5

When the body of a patient, who has a long standing mixed nerve lesion, is heated up in a warm chamber, the arms remaining exposed to the atmosphere of the cool room, the temperature of the fingers that have lost their nerve supply does not rise with that of the unaffected fingers, but remains unchanged (Fig 7) In this respect the cases differ sharply from those in which the motor nerves are alone degenerate, and resemble those in which sympathectomy has been done As in simple sympathetic

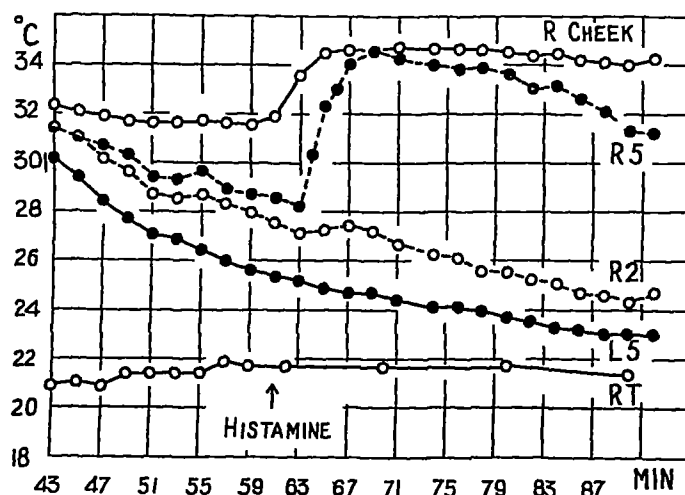


Fig 8 L B, severed his right ulnar nerve on July the 14th, 1931 By the 20th of July the right ulnar area showed persistent coldness, and the histamine flare and ice reaction could not be elicited when tested in the 5th finger On this day the patient was given 1 c c of histamine acid phosphate subcutaneously, in the resultant flush, the right but not the left little finger showed a rise of temperature with palpable pulsation of its digital vessels

The present chart illustrates a repetition of this observation on January the 20th, 1932 The hands of the patient were soaked for 17 min in water at 35° , were dried, and exposed While their temperature was falling the histamine was given The face flushed freely, the ulnar area of the right hand became bright red in colour The left hand altered little in colour and its temperature showed no response The chart shows the response of the right little finger (R5) while the temperature of the right index finger (R2) and of the left little finger (L5) continued to fall

degeneration, a subcutaneous injection of histamine has been found to raise the temperature of the affected finger especially (Fig 8) But although there is this common lack of response to central heating and a similar reaction to histamine in the two types of case, one of which has lost all nerve supply and the other sympathetic fibres only, these two types contrast in that while loss of sympathetic supply causes the corresponding fingers

to be in general warmer than they otherwise would be, loss of all nerve supply causes the corresponding fingers to be in general colder than they otherwise would be. And, since with combined loss of both motor and sympathetic supply the digits remain warm,* it seems that sensory nerve loss must be an important factor in determining the persistent coldness in cases of mixed nerve lesion. This idea, first expressed in an earlier paper (12), has received recent support from the experiments of Zuckerman and Ruch (19) who found that in the monkey a completely denervated hind limb was persistently colder than a hind limb innervated only by the posterior root system. Loss of the posterior root system might lead to vasoconstriction in the corresponding territory either by cutting off vasodilator impulses normally travelling from the cord along these fibres, or by loss of an axon reflex normally active in maintaining bloodflow through the skin. If loss of the sensory axon reflex is a chief factor in its production, then coldness of the anaesthetic skin should be first evident at or about the time when the sensory fibres degenerate.

The time at which the fingers become cold after mixed nerve lesions. The first observations upon temperature changes in the finger following complete loss of nerve supply were made on K R (12, page 188). This was a case of transection of the right ulnar nerve at the elbow in a girl of 14 years. When examined both on the 2nd and 3rd days after injury the 5th was palpably the hottest finger on the right hand, an observation confirmed by thermoelectric measurement. But 21 days after injury it had become the coolest of the fingers and it remained so for long afterwards. In this patient it was also noticed that the reaction of the finger by vasodilatation, subsequent to and in response to immersion in very cold water, was present on the 3rd day but absent from the 21st day onwards, the flare reaction to histamine introduced into the skin behaved similarly. The warmth of the finger on the days immediately following nerve section was attributed to loss of sympathetic nerve supply, the later development of coldness was thought to be connected with degeneration of the sensory cutaneous nerves and loss of the corresponding axon reflex. It was pointed out that since this axon reflex gives vasodilatation in response to considerable cooling, it tends to protect the skin of the fingers from excessive cold and, for this and perhaps other reasons, very probably keeps the temperature of exposed parts above that which would otherwise prevail. Patients subsequently studied have afforded confirmatory evidence of the time at which the hot finger becomes cold. Thus in a patient (L G) the ulnar nerve was severely damaged during the manipulation of a rigid elbow. Anaesthesia and analgesia were complete in the corresponding area of skin and the corresponding muscles

* This statement is based on the effects of sympathectomy in our two cases of anterior poliomyelitis. Although we cannot say that in either case there was a complete lesion of the motor nerves, yet the extent of the lesion was much greater than after section of a single mixed nerve. In both patients the motor nerve lesion had abolished movements of the toes and rendered those of the ankle very feeble, it had led to gross muscular wasting below the knee and to a pronounced coldness of the affected limb.

were fully paralysed. The ulnar area was found hotter than the rest of this hand 7, 8, 9 and 11 days after injury. Eight days after injury, the reactions to histamine and to ice were tested and found intact. On the 13th day the patient thought the 5th finger had cooled, on the 14th day it was definitely ascertained to be cooler than the rest of the fingers of the hand, and it remained so for the rest of observation (up to the 59th day). On the 14th day the histamine flare was tested and found to be still present but decidedly reduced in extent. On the 15th day a little recovery of anaesthesia and of muscular power was noted, and this progressed, about the 24th day the condition became stationary, there being still much loss of sensation over the whole area, and weakness persisting in the adductor pollicis, the interossei, and hypothenar muscles. The flare to histamine never disappeared in this patient though it became greatly diminished. The reaction to ice on the 22nd day was present but reduced (3° rise as compared with 8° rise on the 8th day). Thus, the onset of coldness in these fingers coincided closely with the reduction of the axon reflex between the 11th and 14th days, the reduction being due presumably to degeneration of most but not all the fibres of the damaged ulnar nerve. A patient, L B, severed his ulnar nerve at the elbow by falling on a bottle, the ends of the nerve were found and sutured together. His fingers were thoroughly and frequently tested. His histamine flare was lost over the anaesthetic area on the 8th day, the reaction by vasodilatation in his 5th finger in response to cooling was reduced on the 9th day and almost lost by the 13th day. The finger was at first hotter than the others, on the 11th day it was first noticed to be definitely colder than the others, and it remained so subsequently.

These observations show that the onset of coldness in a finger deprived of all its nerve supply comes at or about the time when the nerves to the fingers degenerate. We believe the development of coldness of the finger to be associated with this nerve degeneration and probably with loss of the sensory axon reflex. That it is unconnected with sympathetic degeneration is apparent from the behaviour of the fingers in cases of sympathetic ganglionectomy, for in these coldness of the fingers does not develop. The precise mechanism by which the vessels locally assume their greatly increased tone after mixed nerve degeneration is perhaps still not entirely clear. A case that has received close consideration is the following. A boy (F S), injured his median nerve. Six weeks later, the paralysis being still complete, the affected fingers were cold and exhibited neither flare nor reaction to severe cold (*see* Fig 10 of an earlier paper (12)). These observations are in full accord with those already given. The boy was kept under observation for a long time to ascertain the order of events during the stage of recovery. Recovery began about 10 months after injury, sensation and movement being normal at 13 months. Simultaneously the histamine flare returned in full force, and vasodilatation of usual degree in response to immersion in ice cold water could be obtained in the fingers of both hands. At the 15th month, the reaction of the fingers was tested to water at 7°C , a tempera-

ture which gives a weaker reaction than does 0° , thus forming a more sensitive test, the reaction was a conspicuous one and equal on injured and uninjured sides. There was, however, a distinct delay in the recovery of natural warmth by the originally affected fingers, these fingers, namely, 1, 2 and 3, remained colder than any other fingers of either hand at this time. Relative coldness of these fingers persisted for at least 2 months after full recovery of sensation and of sensory nerve reflexes. The coldness, however, was inconstant in its later stages, the hands warming up to equal high temperatures when the boy's body was warmed, and the hands becoming equally moist with sweat, before long the fingers became normally warm in all circumstances. The discrepancy in the times of recovery may prove unimportant, but it remains at present unexplained. The questions of muscular atrophy and disuse were fully considered at the time, and we were assured that the fingers of both hands were being used equally, the boy engaging in many active games in which the hands were employed, there was still, however, slight wasting of the thenar eminence on the injured side. The condition of the vessels was also examined to try to ascertain if during the long period of increased vascular tone any structural disease had occurred in the vessels of the cold fingers. The pulsation of the vessels of the injured and control fingers when heated to 45° was found equal both by palpation and also by measurement with the optical capsule (*see next page*). A very similar series of events was observed in the recovery of the ulnar nerve lesion of K R. In this girl both the reaction to histamine and to ice returned in 13 months. The 5th finger, though warming in response to warming of the body, was colder than the rest from time to time for over 2 years, in this patient, however, recovery of sensation was never complete.

Some doubt that a full explanation has been obtained of the cold fingers in mixed nerve lesions has arisen out of Grant and Bland's recent investigations of the rabbit's ear (5), in which vasodilatation in response to cold appears to be to a large extent independent of an axon reflex. It is to be stated, however, that denervation does not give rise to subsequent coldness of the rabbit's ear as it does in human fingers. The evidence for the original conclusion that in man sensory nerve degeneration abolishes the local vascular response to cooling has been revised closely, by repeating the observations on fresh cases. Fresh observations have been made in which the responses of the normal and denervated fingers have been compared after first bringing the fingers to equal and normal temperatures, and while the body of the subject has been warmed. The reactions have also been compared while the subject has been flushed by subcutaneous injection of histamine. These tests were made to see if the loss of reaction to severe cold is a matter merely of original coldness of the finger with high tone in its vessels. But in none of them has the denervated shown any significant reaction (greater than 1°C), therefore, we still attribute the normal reaction to a sensory axon reflex in man. Resolution of the seeming inconsistency between observation on man and rabbit and of the minor discrepancy connected

with the times of recovery of warmth and axon reflex remains for future investigation

The evidence at our disposal indicates that the persistently diminished bloodflow through the affected fingers after mixed nerve section is the result of the following three separate factors, which increase the tone of the arteries and arterioles and which are cumulative in their action —

(a) The chief cause of the lowered skin temperature after mixed nerve lesions is loss of the fibres belonging to the posterior root system. While it is probable that this loss is effected chiefly through the disappearance of the sensory axon reflex, we are unable to exclude the possibility that loss of vasodilator impulses passing from the cord by posterior root fibres may also play a part

(b) Loss of sympathetic supply is followed by a compensatory change, which increases vascular tone

(c) Loss of the motor nerve supply leads to inactivity of the corresponding muscles which tends to lower skin bloodflow, probably owing to relative cooling of the affected muscles

Thus the mechanism of vascular changes in mixed nerve lesions is complex. In long standing cases there is further to be added the possibility of structural disease in the vessels, which will now be briefly considered

Arterial disease To test the state of the arteries in the affected fingers, the freedom of their pulsation has been measured by using a capsule and optical recorder described in a previous paper (11), the amplitude of pulsation being used to indicate the degree to which the vessels will dilate under local heating. Both hands are deeply immersed in water successively at 30°, 35°, 40° and 45° for several minutes before and during each test, the immersion at 45° soon producing a generalised cutaneous vasodilatation through the vasomotor nerves in addition to the local dilatation from direct heating. A comparison has been made between a denervated and the corresponding normal finger of the other hand in 3 cases (J S, T R, and J W, aged respectively 16, 26, and 31 years) of median nerve section of 13 to 15 months' duration, and in one case (L C, aged 18 years) of ulnar section of 3 years' duration. Fig 9 shows that the volume pulsation (in c mm per 10 c c of tissue) is less in the denervated finger (broken lines) than in the corresponding normal finger (unbroken lines) in each subject. The decrease is probably not due to loss of sympathetic supply for in a patient, seen after a left cervico-dorsal sympathetic ganglionectomy for a chilblain condition of the index and middle fingers 20 months previously (Case 1 of previous report (14)), the ring fingers showed equal pulsation on the two sides over the temperature range here considered. The decreased volume pulse is similar to that found in moderately severe Raynaud's disease (11 and 15) in which it has been ascribed to structural change (intimal thickening) in the vessels. An atrophic condition of the fingers reminiscent of that in Raynaud's disease was present in greater or lesser degree in all

four of the cases of nerve section tested, in three the tension of the skin of the affected fingers was a little, and in one (J W) much increased. These observations suggest that in cases of old standing peripheral nerve section the vessels undergo structural disease leading to a permanent defect in vascular supply, but a final conclusion is unwarranted in the absence of histological evidence, which must be awaited.

Changes in the appearance of the fingers Two or three days after section of the ulnar or median nerve the anæsthetic skin is dry but otherwise is

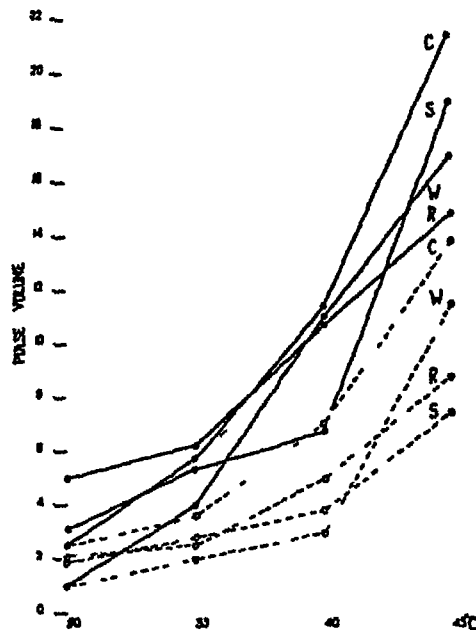


Fig 9 Optical measurements of the pulsation in symmetrical fingers, normal (unbroken line) and anæsthetic (broken lines) from four patients, in whom peripheral nerves had been severed. Each reading was taken after soaking the hands for 5 or more minutes in water at the corresponding temperature (30°, 35°, 40° or 45°). The amplitude of pulsation is given in c.mm per 10 c.c tissue.

- | | | |
|---|---|---|
| C | Left ulnar nerve severed above elbow 3 years previously | Readings from right and left 5th fingers |
| S | Left median nerve severed at wrist 13 months previously | Readings from right and left 3rd fingers. |
| R | Left median nerve severed at wrist 15 months previously | Readings from right and left 3rd fingers |
| W | Left median nerve severed at wrist 15 months previously | Readings from right and left 2nd fingers |

usually normal in appearance. If the hand has been exposed, then by about the 10th day, the anæsthetic skin may show a little thickening and flaking of its horny layer, a condition described by Head and Sherren (8). This condition, which is also seen after sympathectomy, is probably chiefly due to dryness of the skin resulting from loss of sweating, if the hand is soaked

in water, these flakes become sodden and peel off when the hand is dried, revealing a surface which closely resembles that of the skin retaining its innervation. The later changes develop gradually.

One of the earliest changes after the anæsthetic skin has become persistently cold is a gradual deepening of its colour and a tendency to cyanosis, this change is often evident by the second month after section. Over the affected fingers the skin loses many of its wrinkles, especially so over joints that are unused, and becomes slightly more shiny than that of the corresponding fingers of the unaffected hand. The more profound changes, which are confined more or less closely to the anæsthetic territory, consist in atrophy of the skin and soft parts of the fingers, and in changes in the form of the nails (Figs 10, 11 and 13), these changes are often evident by the 4th month, and become pronounced within 12 to 18 months, in patients in whom the nerves have regenerated within 12 months the changes are much less conspicuous. The superficial layers of the skin are demonstrably thinner than they should be and the skin often gives the impression of increased transparency. The difference between normal and abnormal skin is best displayed by soaking the hand in water at 40° for 10 or 15 minutes, or in warm alkaline solution for a shorter time, in these circumstances the superficial layers swell by imbibition (*see note on page 173*) and become thrown into larger or smaller folds and are rendered opaque. The soft parts shrink, the finger becomes more slender and pointed. The atrophy is most noticeable in the pads of the fingers, which no longer project beyond or far beyond the end of the nail-bed. The nails become narrowed and clawlike, being excessively curved laterally and anterior-posteriorly, a change associated with and probably due to loss of subcutaneous tissue from the end of the finger, their rate of growth is decreased. The bones of the affected fingers, and to a rather less extent of the other fingers of the affected hand, become rarefied and in long standing cases decreased in size.

Injuries and healing Since the affected fingers of the patients discussed are insensitive to pain stimuli, they are more than normally subject to injury, and especially to injury by contact with very hot objects. They are also more prone to acquire chilblain than are the corresponding fingers of the normal hand. These lesions produced by injury, and these chilblains, heal more slowly than is normal.

THE MECHANISM OF DIGITAL CHANGES IN VARIOUS DISEASES

Most of the changes that occur in the limbs of patients suffering from diseases of the nervous system, in so far as these have been brought under the terms "vasomotor" and "trophic" will be found under the following sub-headings. We shall attempt to show that each of these changes is susceptible of a simple explanation, which if not final is yet supported by substantial evidence.

Atrophy of the fingers We mean by this term a condition in which the digits become thin and tapered, and in which the pads are lost and the nails

over-curved, the soft parts are obviously shrunken, the bones are rarefied and may be reduced in size. These changes occur in a number of diseases, characterised by prolonged immobility, whether this results from fixation of joints or tendons or from paralysis of the muscles of functional or organic nervous origin, they occur particularly when the peripheral nerves are divided. As previously stated, two possible causative factors are in general common to patients presenting these lesions, namely, disuse itself and reduced bloodflow. In discussing those lesions in which the reduction in bloodflow is intermittent, we have given reasons for thinking that disuse is ordinarily a more important cause of digital atrophy than is reduced bloodflow. But in lesions of the mixed nerves, disuse alone will not explain all the atrophic changes observed. They are too sharply defined. Atrophic areas of skin following nerve lesions may often be demonstrated by soaking the hand in water, and from time to time instances are seen in which after such immersion the anæsthetic area seems to be almost sharply mapped out by the crinkling of the neighbouring normal skin. The first instance in which this was observed was in a boy, F S, 2 months after his median nerve had been severed. After immersion conspicuous crinkling was seen upon the sensitive 4th and 5th finger tips, but none on the insensitive tips of digits 1, 2 and 3. The ulnar half of the palmar surface of the hand was covered with fine crinkles, the median half was uncrinkled, crinkled and uncrinkled skin were almost sharply separated by a line extending from the centre of the wrist to the base of the 3rd finger, a line which with minor discrepancies marked the separation of anæsthetic from sensitive skin. The line of separation is not always so clearly defined as in this instance, nor do the uncrinkled and anæsthetic areas always correspond so precisely, nevertheless their occasional almost sharp correspondence indicates that the atrophy of the skin cannot solely be the result of disuse, for it is inconceivable that in the palm of the hand used and unused skin can correspond closely with sensitive and insensitive skin. The close correspondence between the areas of cold and of anæsthesia and atrophic skin after nerve section suggests that in these cases deficient blood supply may play an important part in producing the atrophic changes. Support for this idea may be obtained by considering maladies in which the vessels are diseased. The fingers of severe cases of Raynaud's malady often show changes very similar to those in lesions of peripheral nerves, they become thin and tapering, the pulp disappears and the nails curve, the growth of the nails is slow and the skin is thin and acquires unusual smoothness, the bones are less dense to X-ray penetration than are those of a normal hand, and those of the terminal phalanges are often shortened. Such changes cannot be explained by loss of substance through necrosis, occurring as they do as diffuse changes in fingers in which external loss of tissue has been quite local and trivial, or has never occurred. They are not due to disuse, here we have particularly in mind a case of Raynaud's disease under our care, in whom atrophic changes of the fingers are distinct (Fig 14), and who is a seamstress earning her livelihood by using

her hands. But her fingers for many years have been for most of the hours of each day at room temperature, during which the bloodflow through them often stops, or is only just perceptible. We also have in mind cases of thromboangitis affecting certain digital arteries and resulting in similar atrophy of corresponding fingers. One of our cases of this malady had lost both feet but was scarcely aware of the condition of his left hand until his attention was drawn to it. The ulnar artery was impervious and the circulation to all fingers, but especially to the 3rd, 4th and 5th, demonstrably defective, as evidenced by temperature, reactive hyperæmia, and other tests. The man regarded this hand as fully serviceable and used it as freely as his right one. But the left fingers, when compared with the right, were distinctly small and tapered, the pads of the fingers, especially of those chiefly affected, were distinctly atrophic (Fig 15), the skin was abnormally smooth and a little but definitely deficient in mobility, its blood colouration was increased.

The results of our observations on the causes of digital atrophy may be summed up as follows. In those conditions in which the sympathetic and sensory fibres remain intact and where the vessels are free from disease, the reduction of bloodflow is of the intermittent type discussed on page 156 and is rarely sufficient to be more than a secondary factor in producing atrophic changes, the more potent factor in these conditions is disuse. In such cases the atrophic changes develop at a rate that is relatively slow and proportional to the extent and duration of the disuse, they rarely become severe except in old-standing cases of almost complete disuse. In maladies where the reduction in bloodflow is considerable and persistent, as in severe Raynaud's disease and thromboangitis, this reduction in bloodflow may be the sole cause of atrophic changes. The relatively rapid development and ultimate severity of the atrophic changes seen after peripheral nerve injuries may be attributed to the operation of both factors, namely, to disuse and to a persistent and considerable reduction in blood supply.

Information relevant to the influence of disuse and of blood supply on the growth of epidermal tissues may be obtained by measuring the growth of the nails marked by nitric acid. Head and Sherren (8) showed conclusively that there is a close relationship between growth and use. This relationship appears in most cases to be independent of the discontinuous reduction in blood supply to the limb which disuse entails. Thus in the two patients with poliomyelitis, the nails continued to grow more slowly on the paralysed than on the normal side, even after the affected foot had been rendered persistently warm by sympathectomy. Again in one of the patients with progressive muscular atrophy, in whom the affected hand was used, the nail growth was equal on the two sides in spite of the tendency to coldness of the affected hand. When, however, the reduction in bloodflow is considerable and persistent, it may be associated with a decreased nail growth, even in the absence of disuse. Thus in the seamstress already described as suffering severely from Raynaud's disease, the nails grew

at the abnormally slow rate of 0.4 mm per week (normal = 0.7 to 1 mm per week). Again, in the patient with thromboangitis described on page 171 the nails of the affected 5th finger grew at 0.6 mm per week as compared with the rate of 0.9 mm per week for the corresponding normal finger of the other hand. We have as yet met with no instance where sympathectomy has increased the rate of nail growth in an otherwise normal limb, but it is probable that such instances do occur, for in the rabbit sympathectomy has been found to increase ear growth, by Harris and Wright (6), and the rate of hair growth on the ear by Grant (4).

Smooth skin It is perhaps advisable here to avoid the use of the term "glossy skin" as it has come to be associated especially with skin presenting very brilliant light reflexes, and particularly with the conditions of skin developing in cases of severely painful lesions of peripheral nerves (causalgia), which are not considered here.

After division of ulnar or median nerve, the corresponding fingers may become smoother than formerly and even develop a little gloss. There is more than one factor which affects the surface of the skin in this way. Many of the furrows, large and small, which normally break the smooth surface of the skin, are associated with movement, a movement of extension throwing the skin on the extensor aspect into folds between which the furrows intervene. In any condition of disuse the skin ceases to be thrown periodically into this folded or wrinkled condition, and the corresponding furrows tend to disappear. Thinness of the skin, an atrophic process, will automatically abolish large folds and render furrows finer and less conspicuous. Finally, tightening up of the skin, whether this arises through a change in the skin itself or from swelling of the tissues lying within it, causes the skin to become smooth and may even give it an unusual gloss. The shiny skin of the leg in dropsy is obviously an affair of tension, disappearing as soon as the dropsy subsides. In Raynaud's malady the fingers may be distinctly swollen, and they are then much smoother than normal or actually shiny, a similar state is seen from time to time in disuse. The chief point that we here desire to emphasise is that such changes as are seen in the texture of the skin of fingers in the lesions of the nervous system considered, are readily explained as the outcome of disuse and the malnutrition, which so usually accompanies it.

Other effects of defective blood supply A cyanotic tint of the cold fingers or hand is frequent in many of the types of case discussed, it is due to the slow flow of blood through the skin, which does not differ greatly, if at all, in tint from that of normal fingers at corresponding temperatures.

Increased depth of colour may be brought about by thinness of the horny layer of skin of fingers or palm, which renders the contents of underlying vessels more clearly visible, but the chief reason is that long continued cold permanently dilates the minute vessels. As a temporary effect such a dilatation from cold is often to be noted in normal subjects. Continued coldness, however, leads to a more pronounced and persistent dilatation.

of the minute vessels, a fact to which attention has been drawn already by Haxthausen (7) and by this laboratory (12), in the instances of erythrocyanosis of the shins, prevalent among women since clothing of the legs has become scanty, and in that of the high cheek colour of those exposed in cold windy climates

It may be assumed safely that the vessels of any part of hand or foot, which is deprived of blood supply to an extent that brings its temperature near to that of the surrounding atmosphere for many hours each day, will in time show these changes. Widening of the minute vessels is seen not only in lesions of peripheral nerves, but in syringomyelia, anterior poliomyelitis, in simple disuse, and in conditions primarily involving the blood vessels, for example Raynaud's disease, acrocyanosis and thromboangiitis obliterans. The reddening of the skin as a response to cold may happen with or without manifest signs of inflammation. It is notable that in all the states described the skin may become damaged more acutely with the production of chilblains. When these chilblains occur on skin in which the natural local vascular response is prevented from occurring, as it always is in peripheral nerve lesions and as it often is in Raynaud's disease and other states, then these chilblains are modified, their colour is duller, their swelling is less, and their healing is unusually slow. In cases of erythrocyanosis of the shins, chronic induration of the skin, with nodule formation and indolent ulcers, are not uncommon, and these may be ascribed to injury from cold of tissues in which nutrition is depressed by low temperature and poor blood supply. Slow healing is in fact invariable in skin to which the circulation is much reduced, a statement which applies not only to injuries derived from cold itself but from mechanical and heat injury. In this connection, the rapid cure by sympathectomy of indolent ulcers developed in the paralysed legs of patients with anterior poliomyelitis affords striking evidence of the previous effects of deficient circulation.

Briefly, cold affects the skin in a number of ways. It often damages the skin directly. By benumbing the skin and muscles, where there is not already damage to the nerves, it renders the fingers clumsy and more prone to accidental damage. By diminishing blood supply and nutrition it interferes with the reactions of inflammation and the processes of repair. Cold is responsible for many of the effects hitherto regarded as "trophic" in origin.

Note on imbibition in skin

It is a matter of everyday observation that if the hands are long in warm water the skin becomes thrown into folds. These folds are especially prominent on the finger tips, the furrows between them being deep and long. On the palmar surfaces of the hands the folds are smaller and less distinct, on the dorsal surfaces they are even less distinct. This crinkling of the skin is to be ascribed to the process known as "imbibition" and described in connection with gelatin and fibrin by Hofmeister (9), Ostwald (17), Spuro (18), Fischer (1) and others. Our statement that crinkling of the skin results from the imbibition of water is based upon the following evidence. Crinkling of the skin after immersion is due neither to congestion nor cedema of the skin, it is independent of the blood supply to the part, occurring equally well in the fingers if the circulation to the hand is arrested throughout the period of its immersion. Contact with the warm water is

essential, no crinkling occurs in a finger previously coated lightly with vaseline. In water at about 40 to 42°C slight crinkling is seen in the finger tips in 10 to 15 minutes, it becomes very definite in about twice this period of time. The crinkling occurs much more slowly in water at 20° than at 40°. If fingers of one hand are immersed in water and fingers of the other hand are immersed in $\frac{N}{20}$ HCl, the time taken for crinkling to appear is shorter on the side of acid bath. A similar statement is true of $\frac{N}{20}$ NaOH. If used at 40°, either the acid or alkaline bath will induce well defined crinkling within 3 to 5 minutes. This behaviour of the skin to temperature and to acid and alkali is similar to that described for gelatin and fibrin. The horny layers of the skin swell as they take up water, become whiter and more opaque. If a small piece of horny layer is removed from a finger tip before immersion, the surrounding skin swells during immersion, leaving a central pit. The skin is thrown into folds presumably because the superficial layers take up water and expand, while the deeper layers remain unchanged.

SUMMARY AND CONCLUSIONS

(1) Disuse, whether resulting from lesions of the motor nerves, from fixation of the joints or tendons, or from psychical disturbances, leads to a diminished circulation through the skin of the immobilised part. The mechanism of this change is discussed.

(2) After loss of sympathetic supply, there is some regain of tone by the vessels of the affected limb, but the skin remains in general warmer than the symmetrical normal skin.

(3) After combined loss of motor and sympathetic supply, as in cases of old-standing anterior poliomyelitis subjected to sympathectomy, the affected limb is in general warmer than the unaffected.

(4) Section of a mixed peripheral nerve leads first to abnormal warmth, but soon to persistent coldness of the denervated skin. The change from warm to cold skin seems to correspond in time with degeneration of the sensory fibres.

(5) The reduction in bloodflow through the skin after section of a mixed nerve is due chiefly to loss of the posterior root fibres, partly to regain of vascular tone after loss of sympathetic supply, and partly to muscular inactivity consequent on motor nerve loss. The possibility of organic vascular change in the digital vessels in long standing cases of peripheral nerve section is also considered.

(6) The nutritional changes in the skin, subcutaneous tissues, and bones, are described in a number of patients with lesions of the nervous and locomotor systems. These changes may all be explained by disuse, defects in bloodflow, and sensory loss, and it is unnecessary to assume in explanation any "trophic" influence of the nervous system on these structures.

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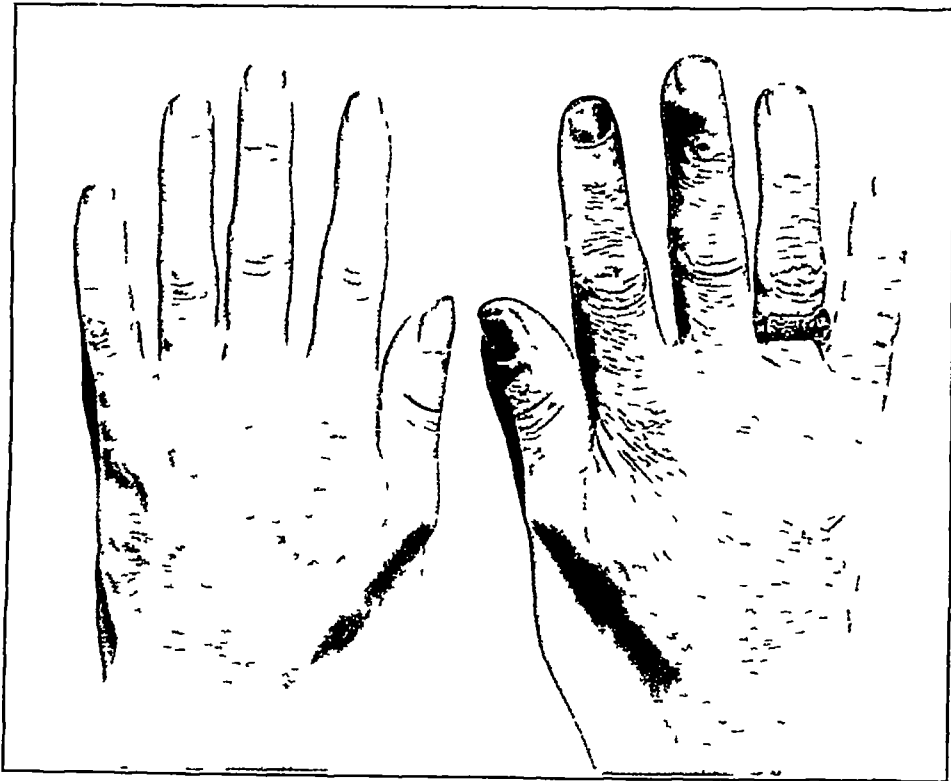


Fig 10 J W aged 31 severed his left median nerve on April the 17th 1929 Photographs taken July the 7th 1930 No recovery of power or of sensation Fingers 1 2 and 3 of left hand cold and anæsthetic (*see* Fig 6) The figure shows the relatively smooth skin of the left hand especially of fingers 2 and 3, the folds in the skin over the interphalangeal joints of fingers 2 and 3 are inconspicuous these fingers the thumb and to a less extent finger 4 are atrophied Fingers 1 and 2 are tapered with loss of pad and increased curvature of the nail

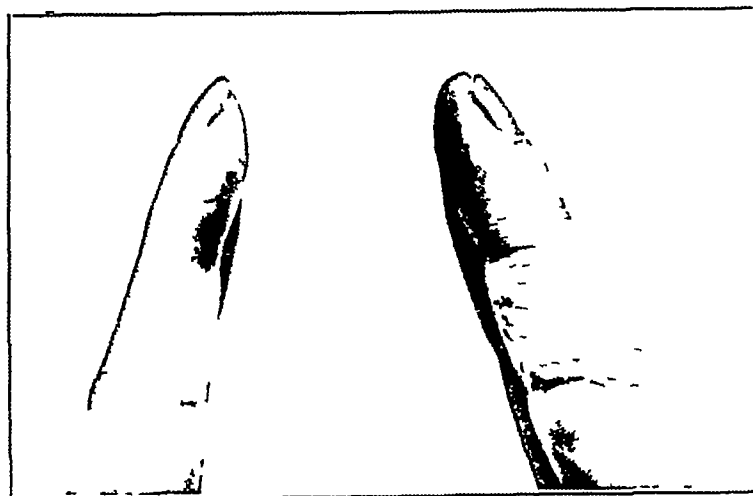


Fig 11 Index fingers of the same subject, photographed from the side. The left finger tapers; its nail is overcurved, all the furrows and ridges of its skin are poorly marked.

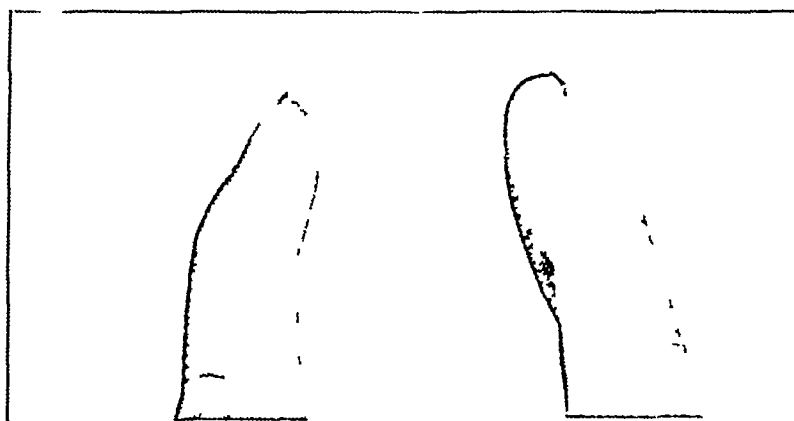


Fig 12 P.T. aged 38, the left hand had been little used for 12 years as a consequence of bullet wound and subsequent fixation of the joints. Despite prolonged disuse the hand was often warm and the fingers showed less atrophy than is frequent in such cases. The atrophic changes shown in the left index finger are, however, characteristic: the finger tapers, its pad is reduced, its nail is a little overcurved, and the skin is relatively devoid of furrows and ridges and therefore smooth.

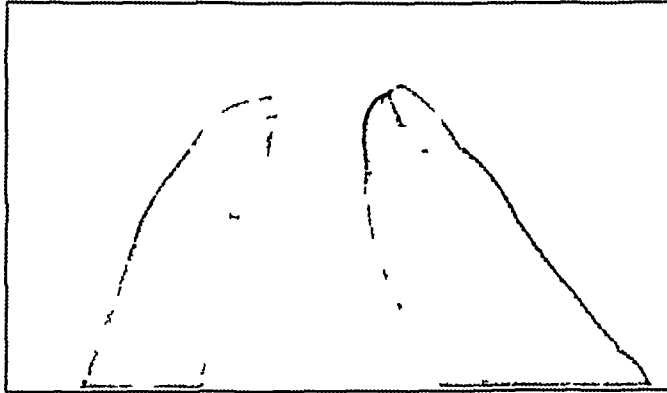


Fig 13 Male aged 37 Photograph taken May 1934 Traumatic injury to left brachial plexus May 1932, with disuse of the arm which was complete for 18 and nearly complete for the last 6 months Sensation lost up to the shoulder at first began to recover at the 18th month the ulnar area of the hand remained anæsthetic All the muscles of the limb were wasted especially the small muscles of the hand The limb was persistently cold for the first 18 months warm only when used for the last six Warming the body gave a normal vasodilator response from the index, none from the anæsthetic 5th finger All the fingers on the affected side showed extreme atrophic changes their bones were less dense to X rays than those of the other hand Photograph shows the two index fingers viewed from the side

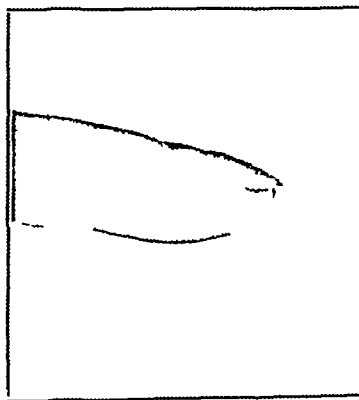


Fig 14 M H, female, aged 57 suffering from severe Raynaud's disease of many years duration Photograph taken in April 1934 shows the left middle finger seen from the side The pulp of the finger is atrophied and the nail overcurved

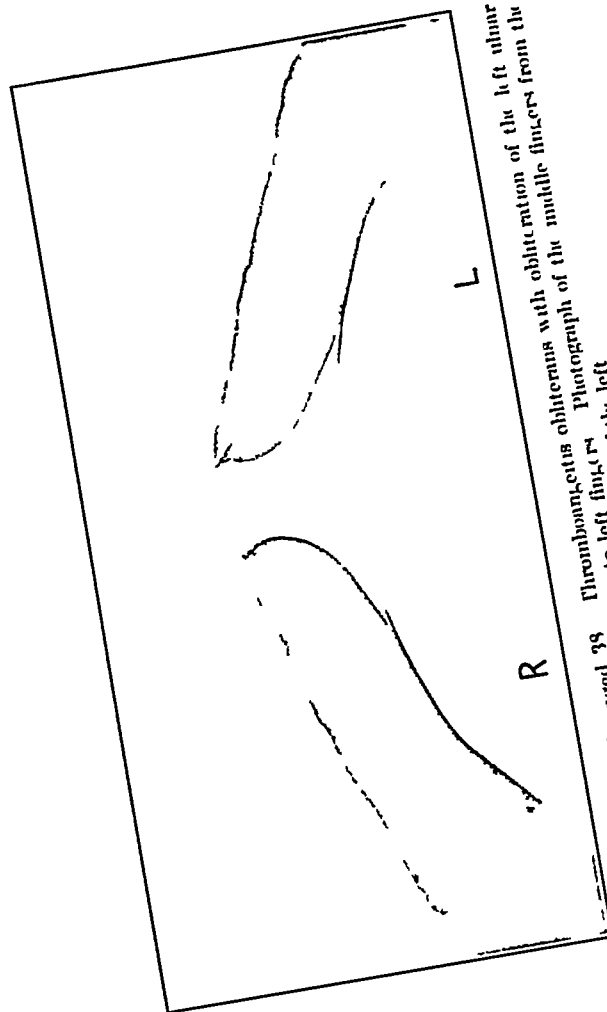


Fig 15 CM male, aged 39 Thromboangietis obliterans with obliteration of the left ulnar artery and deficient circulation to left fingers Photograph of the middle fingers from the side June 1930 showing atrophy of the pad of the left

THE EFFECT OF INTRODUCING BLOOD FROM PATIENTS WITH ESSENTIAL HYPERTENSION INTO OTHER HUMAN SUBJECTS *

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MANY have sought a circulating pressor substance as the agent responsible for high blood pressure in man. Danzer, Brody and Miles (6) claimed that the injection of blood from a patient with hypertension produced a pressor response in cats desensitised by previous injection of the same blood, Curtis, Moncrieff and Wright (5) using the same method, obtained no pressor response from the blood of five hypertensive patients. Bohn (3, 4) claims that either an alcoholic extract or an ultrafiltrate of blood from patients with pale hypertension produces a rise of blood pressure in anaesthetised cats, but that similar preparations from normal subjects or from patients with red hypertension produce only a fall of blood pressure. De Wesselow and Griffiths (7), Page (15), and Aitken and Wilson (1), in many careful experiments have been unable to confirm Bohn's results. Kurc, Nakaya, Murakami and Okinaka (12), working with the Trendelenburg frog preparation, claim to have detected a labile vasoconstrictor body, believed to be adrenaline, in arterial but not in venous blood of individuals with normal and raised blood pressures, the adrenaline concentration to which this pressor substance corresponds is in normal subjects 1 in 2 million, in essential hypertension 1 in 600,000 to 1 in 1 million, and in "Schrumpfwere" 1 in 1,200,000 to 1 in 1,400,000. While he did not take the elaborate precautions to avoid oxidation used by the previous workers, Hulse (11), using the same preparation, was unable to detect any vasoconstrictor substance in the arterial or venous blood in red or pale hypertension, although he could detect adrenaline in the arterial blood of normal subjects after intravenous injection of 0.2 mg. Again, Hantschmann (9), using diluted blood on the rabbits' ear preparation, claims that a vasoconstrictor substance which is not adrenaline is present in the blood of subjects with essential hypertension, and to a less extent in the blood of patients with nephritic hypertension. Lastly, Lange (13) claims to have

* Work undertaken on behalf of the Medical Research Council

extracted from human blood and urine a depressor substance unlike those already known, in essential hypertension the concentration of this substance is diminished in the blood and increased in the urine, in pale hypertension it is increased in the blood and diminished in the urine

The results obtained by previous workers are thus confusing and contradictory, moreover, the methods used are open to a number of objections. In the first place it was shown by O'Connor (14) that vaso-active bodies are released during clotting, and lately Freund (8) has shown that at least two substances are formed, namely, a dilator, appearing early, and a constrictor, appearing later. It is probable, therefore, that the depressor and pressor bodies found by some workers in serum or blood extracts are artefacts, that is to say, substances which are bound and inactive in the circulating blood and which are first liberated during clotting or extraction. Secondly, it is possible that a vaso-active body may be destroyed or lost during the process of extraction or ultrafiltration, De Wesselow and Griffiths (7) found, for example, that adrenaline, added to whole blood, could not be recovered in its ultrafiltrate. These objections, and also the difficulties inherent in testing human blood or plasma in the experimental animal, can be avoided by transfusing blood from patients with hypertension into other human subjects, and it is surprising that only Høst seems to have used this method. Høst (10) says that he has performed many transfusions with blood from patients with high blood pressure without observing any effect on the blood pressures of the recipients, and as his only example states that he transferred 700 c c of blood from an eclamptic patient with a systolic blood pressure of 270 mm Hg to a patient with carcinoma of the stomach, who showed no rise of blood pressure on that or on the succeeding day.

The following observations on the effects of transfusion begun in ignorance of Høst's fully confirm his statement, they are summarised in Table I (normal donors) and Table II (donors with essential hypertension). The chief features of the donors with hypertension are summarised at the end of this paper. All the transfusions were done for therapeutic reasons, relevant details relating to recipients are given in the tables. The transfusions were carried out as follows. Blood was drawn from a vein of the donor into a warm flask containing 10 c c of a 20% solution of sodium citrate per 250 c c of blood, this operation taking 5 to 10 minutes. The blood was then introduced into a vein of the recipient, preceded and followed by saline. The recipient's blood pressure was measured by the auscultatory method during, and for several minutes before and after, introducing the blood. The tables show the readings at the beginning and end of the introduction of blood and the change. They also show the time that elapsed from the end of withdrawal to the beginning of insertion of the blood, and the time taken to introduce the blood into the recipient.

It will be seen from Table I that 400 to 550 c c of blood from 5 normal donors introduced into 5 anæmic recipients in 6 to 26 minutes produced rises of systolic pressure varying from 0 to 16 mm Hg and of diastolic

pressure varying from 6 to 15 mm Hg. The greatest rises were observed in two patients aged more than 50 years. So small a rise in arterial pressure suggests that the introduction of this large volume of fluid was accompanied by a corresponding increase in the capacity of the circulation, and it is noteworthy that in all cases the blood content of the skin vessels increased during the transfusion, the colour of the face and hands deepening much more than could be accounted for by increase in hæmoglobin content of the blood. The venous pressure was not measured directly, but from inspection

TABLE I

Shows the effect on the recipient's blood pressure of transfusion of blood obtained from normal subjects

Recipient			Volume introduced in c c		Time in min		Blood pressure mm Hg					
Age	Disease	Hb %	Blood	Saline	From with drawal	To introduce	Beginning		End		Change	
							S	D	S	S	S	D
44	Melæna	52	500	200	—	11	118	74	124	80	+ 6	+ 6
71	Hæmatemesis	34	400	300	47	26	112	60	122	66	+10	+ 6
53	Melæna	24	550	200	—	12	114	60	130	75	+16	+15
24	Carc vent	48	500	200	28	10	122	72	124	80	+ 2	+ 8
40	Leukæmia	24	500	400	22	6	122	60	122	68	0	+ 8

TABLE II

Shows the effect on the recipient's blood pressure of transfusion of blood obtained from donors suffering from essential hypertension

Donor*	Recipient			Volume introduced in c c		Time in min		Blood pressure mm Hg					
	Age	Disease	Hb %	Blood	Saline	From with drawal	To introduce	Beginning		End		Change	
								S	D	S	D	S	D
1	24	Carc vent	62	400	150	10	4	122	70	118	75	— 4	+ 5
2	24	Carc vent	64	350	150	14	5	122	70	125	78	+ 3	+ 8
3	40	Leukæmia	27	550	200	21	8	136	60	138	68	+ 2	+ 8
4	40	Leukæmia	33	400	100	8	4	126	70	125	76	— 1	+ 6
5	33	Peritonitis	50	600	300	4	6	135	65	135	65	0	0
6	40	Melæna	20	500	200	1	7	138	84	137	85	— 1	+ 1
1	32	Carc vent	25	400	150	16	9	116	58	123	66	+ 7	+ 8

* The numbers in this column refer to the summaries of these patients appended to this paper

of the neck veins appeared in most cases to be raised 2 to 4 cm by the transfusion. It may be recalled that Bayliss and Starling found that in a dog intravenous injection of 500 c c saline raised the arterial pressure from 102 to 120 mm Hg and the pressure in the inferior vena cava from 33 to 255 mm H₂O, and concluded that the relatively small rise of arterial pressure and the relatively great rise in venous pressure showed that most of the blood was accommodated on the venous side, a process which they attributed to arteriolar dilatation.

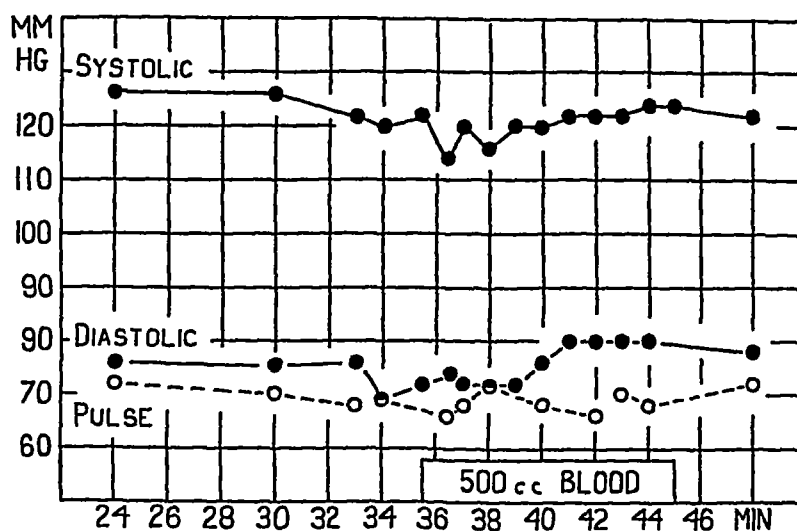


Fig 1 Recipient, a male aged 24 years, suffering from carcinoma of the stomach (Hb = 48%) Shows the systolic and diastolic blood pressure (in mm Hg) and the pulse rate (per min) before, during, and after transfusion of 500 c c blood obtained from a normal subject. The blood was withdrawn between zero time and the 7th minute. The needle was inserted into the recipient at the 28th minute. 150 c c saline were run into the recipient between the 33rd and 35th minutes, followed by 500 c c blood and 50 c c saline between the 35th and 45th minute.

In Table II are summarised the results of seven transfusions, in which 350 to 600 c c of blood from donors with hypertension were introduced in 4 to 9 minutes into anæmic recipients. The changes in systolic pressure varied from a fall of 4 mm to a rise of 7 mm, and of diastolic pressure from 0 to a rise of 8 mm Hg. The changes in skin colour and in the neck veins were similar to those seen when blood from normal donors was used. In each of the recipients receiving blood from donors with hypertension, the blood pressure was again measured after 2 and 24 hours, these pressures were a little lower (5 to 15 mm Hg systolic) than immediately before the transfusion, a difference probably attributable to excitement associated with this procedure.

It is evident from this brief summary that the transfusion of blood from subjects with hypertension produced rises in blood pressure that were in

general slightly less than those resulting from transfusion of blood from normal donors. Two recipients received one transfusion from a normal donor and two from donors with hypertension, and it will be seen from inspecting the tables, that similar changes in arterial pressure were produced by the bloods from the two kinds of donors. The results of two transfusions on one of the recipients are shown in greater detail in Figs 1 and 2.

These results suggest that the blood of patients with essential hypertension is similar to normal blood in its content of pressor and depressor substances. But before taking up any definite position on this question it will be well to consider some objections. First, it might be

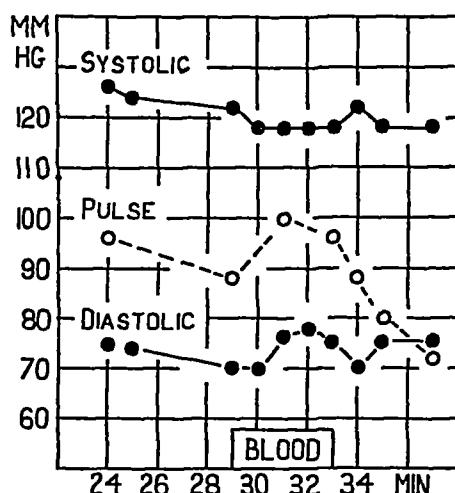


Fig 2 Same recipient as that of Fig 1 (Hb now 62%) Shows the response of the recipient to transfusion of 400 c c of blood withdrawn between zero time and the 10th minute from a male aged 41 with systolic and diastolic blood pressures of 216 and 130 mm Hg respectively (Case 1). The needle was inserted into the recipient at the 26th minute and 100 c c saline were introduced between 28th and 29th minutes. The blood, followed by 50 c c of saline, was introduced between the 29th and 33rd minutes.

supposed that the recipients, being ill, were unable to respond to any pressor substances present in the blood they received. None of these recipients were, however, gravely ill at the time of transfusion, all had normal blood pressures, and in those receiving blood from donors with hypertension the ability to give a pressor response to subcutaneous injection of 0.25 mg adrenaline was tested on the day after transfusion with normal results (a rise of 6 to 12 mm Hg in the systolic pressure). Second, it might be supposed that the hypothetical pressor substance in the circulating blood of patients with hypertension is rapidly destroyed. Yet, when the time elapsing from the withdrawal of blood to its insertion was reduced to less than a minute, no definite pressor response was obtained (Table II and Fig 3). Third, it

might be supposed that the dilution of the donor's blood by that of the recipient was great enough to reduce the concentration of the hypothetical pressor substance below the threshold level for its pressor effect. With this possibility in mind the blood from donors with hypertension was introduced as rapidly as possible, reaching 100 c c per minute in 3 instances. One of these instances in which 600 c c of blood was introduced may be considered in detail. If the recipient's blood volume is taken at the normal figure of 3 to 5 litres, then the inserted blood would be diluted 1 in 6 to 1 in 9 after entering the recipient. It seems difficult to believe that a pressor

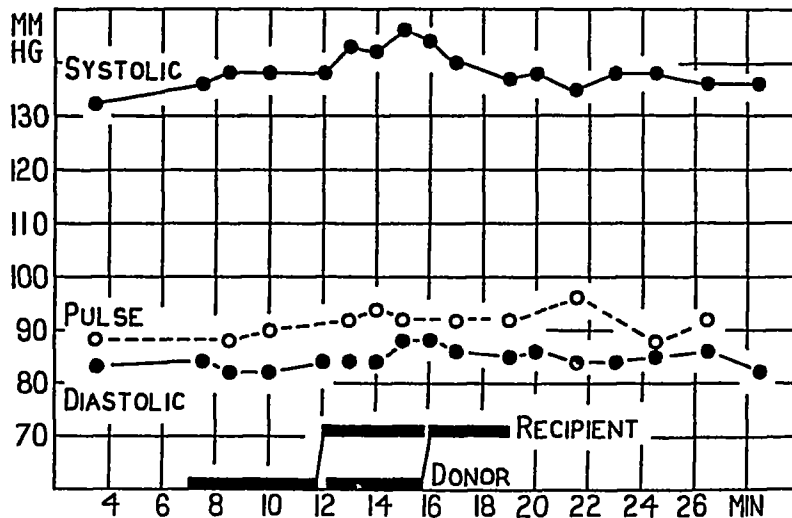


Fig 3 Recipient, a male aged 49 years, suffering from a bleeding duodenal ulcer (Hb = 29%) Donor, a female aged 62, with systolic and diastolic pressures of 240 and 130 mm Hg respectively (Case 6) The transfusion needle was introduced into the recipient at zero time, and 150 c c saline were run in slowly until the 12th minute 250 c c of blood were withdrawn from the donor between the 7th and 12th minutes and introduced into the recipient between the 12th and 16th minutes A second portion of 250 c c blood was removed from the donor between the 12th and 16th minutes and introduced into the recipient between the 16th and 19th minutes

substance, which undiluted in the donor was responsible for systolic and diastolic blood pressures of 240 and 130 mm Hg respectively, should, when diluted in the recipient to 1 in 6 or 1 in 9, produce no pressor effect

To sum up, these observations are opposed to the idea that in so-called essential hypertension, the high blood pressure is due to excess of pressor or to deficit of depressor substance in the circulating blood. They could be made consistent with the view that the high blood pressure in such patients is due to a circulating pressor substance only by supposing that this substance is extremely rapidly destroyed *in vitro* or in subjects without hypertension, or that the substance is inactive in relatively small dilutions. The results do not exclude the possibility that hypertension may be due to the

intervention of a chemical agent which is not circulating but is fixed by the tissues

In conclusion it may be noted incidently that the therapeutic results of using donors with hypertension were quite satisfactory, and the procedure is one that may be commended as likely to benefit both the donor and the recipient

SUMMARY

The changes in arterial blood pressure produced in anæmic subjects by transfusion of blood from patients with essential hypertension are very small and are no greater than those produced by transfusion of an equal volume of normal blood

This result is opposed to the idea that the raised blood pressure in essential hypertension is due to excess of pressor or deficit in a depressor substance in the circulating blood

SUMMARY OF DONORS WITH HIGH BLOOD PRESSURE

The following abbreviations are used —B.P. = systolic and diastolic blood pressure in mm Hg before blood was withdrawn for transfusion Hb % = hæmoglobin content of blood on Haldane scale U.C.T. = Urea concentration test

1 Male, age 41 years, admitted January, 1934 for left hemiplegia B.P. = 216/130, Hb = 106% U.C.T. = 2.5% Eyegrounds slight arteriosclerosis Urine nothing abnormal

2 Male age 40 years admitted January, 1934 for subarachnoid hæmorrhage B.P. = 200/110 Hb = 84% U.C.T. = 1.8% Eyegrounds arteriosclerotic retinitis Urine trace of albumen no excess of red cells Died of cerebral hæmorrhage, June, 1934 Kidneys showed ischemic changes

3 Female aged 48 years admitted February 1934 for attacks of rapid heart action B.P. = 210/110 Hb = 84% Blood urea = 28 mg % Eyegrounds normal Urine nothing abnormal

4 Female, aged 62 years admitted February, 1934, for weakness B.P. = 250/135 Hb = 98% U.C.T. = 2.8% Eyegrounds arteriosclerotic retinitis (since 1932) Urine nothing abnormal

5 Female aged 64 years, admitted June, 1934, for breathlessness Known to have had hypertension since 1926 B.P. = 230/140 Hb = 99% U.C.T. = 2.7% Eyegrounds slight arteriosclerosis Urine nothing abnormal

6 Female, aged 62 years admitted June 1934, for headaches B.P. = 240/130 Hb = 90% U.C.T. = 1.6% Eyegrounds arteriosclerotic retinitis (since 1931) Urine trace of albumen, no excess of red cells

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THE RELATIONSHIP OF THE CAROTID SINUS MECHANISM TO PERSISTENT HIGH BLOOD PRESSURE IN MAN

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THE work of Hering (2) extended by Heymans and his collaborators (6) has shown that in the normal mammal the blood pressure is regulated largely by reflexes originating from end-organs lying in the arch of the aorta and carotid sinus. Denervation of these areas produces a permanent rise of blood pressure and of pulse rate as Koch, Mies and Nordmann (9), Kremer, Wright and Scarff (10), and Heymans and Bouckaert have shown (4). According to recent work from Heymans' laboratory (5) it appears that this hypertension is evident only when the animal is awake and more or less excited, when the animal is asleep or quite quiet the blood pressure is normal. The suggestion has been made that human hypertension may be the result of a disturbance of the carotid sinus and depressor mechanisms and some evidence has been produced for this view. Thus it has been known for many years that in patients with hypertension and sclerotic arteries, pressure over the carotid sinus (vagus pressure of the older authors) may produce an unusually profound fall of blood pressure and pulse rate. Hering (2) found that after cutting the carotid sinus nerves in the rabbit digital pressure over the region of the sinus gave a very large fall of blood pressure and pulse rate, due apparently to stimulation of the free ends of the divided nerves, for pressure on the exposed sinus gave no response. He considered that this resemblance between the responses of patient and experimental animal suggested that in the former there was some interference with the carotid sinus whereby the end organs became less sensitive to intra-sinus pressure and more sensitive to external pressure. Although Hering (3) appears later to have abandoned the view that hypertension in man is due to interference with the function of the carotid sinus and depressor nerves, Mies and Regniers have produced further evidence for its acceptance. Mies (12) investigated 97 patients with high blood pressure and found 17 without renal insufficiency, in these 17 patients, the pulse rate averaged 100 per minute, carotid sinus pressure produced a profound fall

* Work undertaken on behalf of the Medical Research Council

of blood pressure and pulse rate, while obliteration of both carotid arteries below the sinuses gave no rise of blood pressure. In the remaining 80 patients renal function was impaired, the pulse rate was normal, carotid sinus pressure gave a small response, while obliteration of both carotids was usually without effect. He concluded that in the first group of non-renal hypertension the raised blood pressure was due to a disturbance of the carotid sinus and depressor mechanisms whereby they ceased to respond, or responded only slightly to the stimulus of the arterial pressure. Regniers (15) has described 5 cases of hypertension (one with retinitis and one with albumen and casts in the urine) in which carotid sinus compression gave a normal response, while obliteration of both carotids below the sinuses was without effect on blood pressure or pulse rate. He also observed that the bradycardia occurring in normal subjects on release of carotid obliteration below the sinus did not occur in his patients with high blood pressure, and agreed with Mies that in hypertension the carotid sinus did not respond to changes in intra-sinus pressure. In view of these claims and of the undoubted importance of the carotid sinus mechanism in the regulation of blood pressure, we have tested the function of this mechanism, by the methods described by Hering (2), in a number of adult subjects with normal and persistently raised blood pressures.

The patients with high blood pressure were admitted in the ordinary hospital routine, and may be regarded as representative of the cases occurring in this country, for only patients with cardiac failure or uræmia or with necks unsuitable for the tests were rejected. The control subjects with normal blood pressure were selected from the laboratory staff and from convalescent patients in the wards. To simplify presentation the subjects have been divided into four groups—(1) young subjects under 30 years of age, with normal blood pressures, (2) elderly subjects over 45 years of age with normal blood pressures, (3) patients with chronic nephritis and raised blood pressure, these patients were usually under 40 years old and had considerably impaired renal function with persistent hæmaturia, (4) patients with so-called essential hypertension, all these patients were over 40 years old, had normal renal function, no hæmaturia, and no albuminuric retinitis. The tests were carried out with the subjects lying down, and after the blood pressure and pulse rate had settled to steady levels.

Carotid sinus compression. The effects on blood pressure and pulse rate of firm digital pressure over the right carotid sinus for 40 seconds are summarised in Table I. All the compressions were made by one observer and he attempted to use the same degree of pressure throughout.

In judging the significance of the responses to carotid sinus compression shown by the various groups into which our subjects have been divided, two factors have to be taken into account. The first of these is the different initial levels of blood pressure and pulse rate in the various groups. Mark and Neumann (11) have shown that in normal subjects the falls of pulse and respiratory rates produced by sinus compression depend directly on the

initial values of these rates. We have found also that the fall in blood pressure in subjects with normal and raised blood pressures produced by a given dose of histamine is approximately proportional to the initial blood pressure*. To allow for the different initial values of pulse rate and blood pressure, we have expressed in Table I the falls produced by sinus compression as percentages of the initial levels, it will be seen that in each of the four groups of subjects the percentage fall in blood pressure corresponds fairly

TABLE I

Summarises the falls of blood pressure and pulse rate produced in 4 groups of subjects by firm compression of the right carotid sinus for 40 seconds. The figures for age, blood pressure and pulse rate represent the mean for each group

No of subjects	Description	Age in years	Resting blood pressure mm Hg		Resting pulse rate per min	Fall after carotid sinus pressure			
						Systolic blood pressure		Pulse rate	
			S	D		mm Hg	% of resting	Beats per min	% of resting
6	Young normal	21	118	75	78	2	1.7	2	2.6
13	Elderly with normal blood pressure	57	128	76	73	13	10.1	6	8.2
4	Chronic nephritis	28	181	104	81	12	6.7	5	6.2
16	Essential hypertension	59	225	110	77	27	12.0	8	10.3

closely to the percentage fall in heart rate. The second factor is the degree of sclerosis of the carotid arteries. Hering (2) has shown that the fall of blood pressure and pulse rate produced by sinus compression is considerably increased by sclerosis of the walls of the sinus, and his results have been extended and confirmed by Weiss and Baker (16). In our series of cases the percentage falls of blood pressure and pulse rate seem to reflect fairly accurately the extent of sclerotic changes in the larger arteries in the four groups of subjects. Thus sclerosis was absent in the young normal subjects (Group 1) in whom the response was least, present to a slight degree in the nephritic patients (Group 3) in whom the response was greater, and moderate in the elderly subjects with normal (Group 2) and raised (Group 4) blood pressures.

* Intravenous injection of 0.1 mg. histamine acid phosphate produced the following average falls of systolic and diastolic pressures —

- 27 and 19 mm Hg in 6 control subjects aged 29 to 60 years in whom the resting systolic and diastolic pressures averaged 118 and 73 mm Hg
- 49 and 24 mm Hg in 4 patients with chronic nephritis aged 17 to 48 years in whom the resting systolic and diastolic pressures averaged 195 and 110 mm Hg
- 59 and 31 mm Hg in 5 patients with essential hypertension aged 41 to 64 years in whom the resting systolic and diastolic pressures averaged 226 and 126 mm Hg

Expressed as percentages of the initial pressures the falls of systolic and diastolic pressures were 23% and 26% in normal subjects, 25% and 21.5% in chronic nephritis, and 26% and 24.5% in essential hypertension.

The differences in the responses of pulse rate and blood pressure shown by the four groups of subjects thus seem to be adequately accounted for by differences in the initial blood pressure and by the presence or absence of sclerosis of the large vessels. Judged by the size of the response therefore it seems that in our subjects the stimulation of the sinus mechanism produced by a given mechanical compression of the sinus is not related to the presence or absence of hypertension.

The large response to digital compression of the carotid sinus is sufficient evidence of the integrity in human hypertension of the reflex arc whose afferent limb is formed by the carotid sinus nerve.

Compression of one carotid artery below the sinus. More precise information as to the activity of the sinus mechanism is obtained by obliterating one or both common carotid arteries proximal to the sinus, for such obliteration reduces the intra-sinus pressure, and thus alters the intensity of the stimulus to which the end organs ordinarily respond. For the following observations we selected patients whose necks were thin and preferably long, and in whom it was easy to obliterate a carotid artery well below the sinus, without causing much discomfort. In the recumbent patient, one carotid artery was obliterated digitally as low as possible in the neck for a period of 1 minute, and then released. We have no doubt that complete obliteration of the carotid was obtained in each case, for the temporal pulse disappeared on that side throughout compression, and the facial skin on that side often flushed on release. Since the effects of carotid compression might be due, not to any effect on the sinus, but to discomfort or to the mechanical effects of compressing a large artery, we have controlled these observations by pressing on the lateral aspect of the neck and by compressing one femoral artery for the same lengths of time. The effects of these procedures on blood pressure and pulse rate are shown in detail in Table II, the subjects being divided into groups similar to those employed in Table I. It will be seen that in each subject tested, the rise of blood pressure produced by carotid compression was greater than the summated changes produced by the control pressures on neck and femoral artery. The rise of pulse rate produced by carotid compression was also greater than the summated changes produced by the control pressures except in five elderly subjects, two of whom had normal and three raised blood pressure. Finally, release of the carotid compression was followed by a fall of blood pressure and pulse rate as commonly in patients with high as in those with normal pressures. It seems, therefore, that the fall in intra-sinus pressure occasioned by digital compression of a carotid artery produced the same kind of response from the sinus mechanism in our patients with raised and normal blood pressures.

An approximate estimate of the degree of response due to the fall of blood pressure within the sinus may be obtained by subtracting the sum of changes in pulse rate and blood pressure produced by the control procedures from the changes produced by compression of the carotid. The mean

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TABLE II

Shows the changes in systolic blood pressure (S B P) and pulse rate produced by digital obliteration of the carotid and femoral arteries and by pressure on the lateral aspect of the neck for 1 minute in subjects with normal and high blood pressures

Age	Sex	Blood pressure	Rise produced by pressure on						Fall produced by release carotid A	
			Carotid A		Femoral A		Neck			
			S B P	Pulse	S B P	Pulse	S B P	Pulse	S B P	Pulse
1 Young normal subjects										
16	M	128/75	16	6	0	0	7	0	0	0
20	F	102/70	5	4	0	0	0	0	0	0
21	M	123/72	10	8	0	0	1	0	0	4
21	F	110/55	9	5	0	0	4	0	3	4
23	M	125/78	14	16	0	0	4	0	0	0
Average										
20		117/70	11	8	0	0	3	0	1	2
2 Elderly subjects with normal blood pressure										
49	M	114/76	10	4	0	0	0	0	8	0
51	M	110/80	10	8	2	0	—	—	8	0
52	M	140/90	14	10	0	0	0	0	2	2
52	M	122/66	12	8	0	0	4	4	0	6
52	M	130/80	10	1	0	0	0	0	2	0
53	F	118/64	8	2	0	0	6	2	7	0
61	F	136/70	10	6	—	—	8	0	0	8
69	F	125/84	12	4	—	—	6	4	0	0
70	M	135/74	10	—	0	0	4	0	7	0
71	F	132/70	13	3	0	0	0	0	0	4
Average										
60		126/73	10	5	0	0	3	1	3	2
3 Chronic nephritis										
36	M	190/135	22	10	0	4	17	8	0	6
37	F	180/105	24	8	0	0	5	0	0	0
46	M	160/115	22	4	0	0	14	0	0	6
48	F	200/110	14	6	8	0	0	0	8	0
Average										
42		177/116	20	7	2	1	9	2	2	3
4 Essential hypertension										
40	F	174/112	17	15	4	0	6	4	0	0
41	M	240/150	11	8	6	0	4	0	13	2
47	F	240/140	28	8	6	8	0	0	0	0
50	F	260/180	18	8	0	0	10	0	15	4
63	F	220/112	23	1	8	0	6	2	0	0
64	F	210/110	22	10	6	0	10	2	0	0
66	F	220/110	15	0	10	0	0	0	0	0
Average										
53		223/128	19	7	6	1	5	1	4	1

figures obtained in this way are shown in Table III, and are similar in each group of subjects. Physiological experiment has shown that in the normal animal, the end-organs of the carotid sinus are continuously excited by the stretching force of the arterial pressure (1) (2), the rises in pulse rate and blood pressure that occur when the intra-sinus process is lowered by obliterating a carotid are the reflex effects of a diminished discharge of nervous impulses from the end-organs of the sinus (2). The similarity in the size of these reflex responses, which we have observed, suggests that the end-organs of the carotid sinus are stimulated by the resting blood pressure to an extent that is not appreciably less in patients with high than in those

TABLE III

Summarises the rises of blood pressure and pulse rate which, in each group of subjects, may be attributed to a fall of pressure within the carotid sinus. The values are obtained from those in Table II by subtracting the sum of the changes produced by the control procedures from the changes produced by occlusion of a carotid artery.

Description	Effect of lowering intra sinus pressure on	
	S B P mm Hg	Pulse per min
1 Young normal subjects	8	8
2 Elderly subjects with normal blood pressure	7	4
3 Chronic nephritis with hypertension	9	4
4 Essential hypertension	8	5

with normal blood pressure*. Our observations thus provide evidence against the view that the hypertension of chronic nephritis and of so-called essential hypertension is due to an impaired activity of the carotid sinus reflex. It may be noted that Keele (7) has failed to find anatomical changes in the carotid sinus of patients with hypertension that were not present in patients of similar age with normal blood pressures.

The results which we have obtained from carotid compression differ entirely from those previously described by Mies (12) and by Regniers (15). It is possible that the discrepancy is due to a difference in the types of hypertension studied, but we hesitate to adopt this explanation since both these workers, like ourselves, seemingly tested representative examples of patients suffering from persistent hypertension. It seems more probable

* From the results of animal experiments, which show that the stimulation of the carotid sinus end-organs is proportional to the arterial pressure, we might expect that these end-organs would be greatly stimulated in human hypertension. Our evidence is insufficient to say whether this expectation is or is not realised, for the tests of carotid sinus function in man are too crude to admit of this very precise interpretation and the pulse rate is too much influenced by other factors to be a reliable guide.

that the discrepancy is due to a difference of technique. Both Mies and Regniers used compression of both carotids as their test method, and while Mies gives no further details, it seems probable from Regniers' description of his experiments that he failed to obliterate the carotid arteries, for in many of his patients he had difficulty even in palpating them and apparently took no precaution to ascertain whether they were obliterated.

The pulse rate The pulse rate showed only minor deviations from the normal in these patients with high blood pressure, and as Table I shows, the resting pulse rate, averaged for the various groups of subjects, was not significantly different in those with raised and those with normal pressures. It is to be anticipated from the experimental results of denervating the carotid sinus and arch of aorta, that if there were any gross diminution in the activity of these reflexes in human hypertension, tachycardia would also be present. Before the present investigation, we have seen persistent tachycardia in occasional patients with hypertension, it is, however, as yet uncertain how far the tachycardia in these admittedly exceptional cases is to be attributed to alterations in the function of the sinus and depressor mechanisms, and how far to other factors which undoubtedly influence it.

Concluding remarks

The idea that certain forms of human hypertension might be due to an interference with the carotid sinus and depressor reflexes arose from the demonstration that high blood pressure could be produced in the experimental animal by denervating the carotid sinus and arch of the aorta. A comparison of the chief features exhibited by patients suffering from the common forms of persistent hypertension (chronic nephritis and essential hypertension) with those exhibited by the animal with this form of experimental hypertension is instructive, for it reveals differences that are so striking as to leave no doubt as to the essentially different origin of human and experimental hypertension. Thus tachycardia is invariable in the experimental (4, 9, 10), exceptional in human hypertension, compression of the carotid artery below the sinus gives no response in the animal (8, 9) and a definite response in man, sensory stimuli produce a fall of blood pressure in the animal (8, 9) and a rise in man, in sleep the blood pressure falls to normal (5) in the animal and remains elevated in man (13), and lastly, characteristic histological changes in the arterioles are absent in the experimental (10, 14) and usually present in the human form. It is not denied that there may be examples of hypertension in man which are similar in origin to the experimental form, but such cases must be uncommon and we are not satisfied that the evidence for their existence is adequate.

SUMMARY

1 The function of the carotid sinus mechanism has been tested by Hering's method in four groups of human subjects —(1) young adults with

normal blood pressure, (2) elderly subjects with normal blood pressure, (3) patients with chronic nephritis and hypertension, (4) patients with essential hypertension

2 The differences in the response to carotid sinus compression shown by the various groups seem to be entirely accounted for by differences in the initial levels of blood pressure and by differences in the degree of sclerosis of the large arteries

3 Digital obliteration of one carotid artery below the sinus produced, in all subjects with normal and high blood pressure, rises of blood pressure and pulse rate that were greater than those produced by control pressures on the neck and femoral artery

4 The resting pulse rate was essentially normal in the patients with hypertension

5 It is concluded that the hypertension exhibited by patients suffering from chronic nephritis and by most of those suffering from so-called essential hypertension is essentially different in origin to that produced experimentally by denervating the carotid sinus and arch of the aorta

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THE EFFECTS OF ADRENALINE AND OF COLD ON THE BLOOD PRESSURE IN HUMAN HYPERTENSION

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THE following observations on the responses to adrenaline and to cold were undertaken to repeat work which, in the absence of more direct evidence, has come to play a considerable part in forming current opinion as to the mechanism of high blood pressure in man

Material

All the patients with high blood pressure were adults in whom the systolic pressure remained over 150 and the diastolic over 95 mm Hg after rest in bed for several days, all had some cardiac enlargement, none had congestive cardiac failure, signs of retinal arteriosclerosis were present in nearly all cases. Some of these patients, chiefly young adults, had had acute nephritis or had a definite and progressive impairment of renal function with persistent hæmaturia, these patients have been classified as cases of chronic nephritis. The remainder were over 40 years old, had no impairment of renal function or hæmaturia and no albuminuric retinitis and have been classified as cases of essential hypertension. No cases of malignant hypertension or of coarctation of the aorta have been included. Control subjects with normal blood pressures and comparable in age with the two groups of patients with raised blood pressure were obtained from members of the laboratory staff and convalescent patients in the wards.

The subjects were examined lying down under quiet conditions, no interference was made until the blood pressure and pulse rate had ceased to show significant variations for several minutes.

Adrenaline

Hülse (7) has claimed that serum obtained from patients with nephritic hypertension will sensitise the experimental animal to the pressor action of adrenaline, while serum from patients with essential hypertension or from normal subjects will not. Later, Deicke and Hülse (2) claimed that nephritic

* Work undertaken on behalf of the Medical Research Council

patients themselves react unusually profoundly to small doses of adrenaline. Thus they stated that intravenous injection of 0.005 mg produces a rise or fall of less than 10 mm Hg in the arterial pressure and a rise of less than 20 mm H₂O in the venous pressure in normal subjects, in patients with essential hypertension, and in nephritic patients without hypertension, but in nephritic patients with hypertension this dose of adrenaline produces either a greater rise or a greater fall of arterial pressure, and a much greater rise of venous pressure. Hulse (2, 7) has supposed therefore that nephritic hypertension is due to the presence of some substance in the circulating blood which causes the peripheral vessels to react abnormally strongly to normal sympathetic impulses, his results form one of the chief pieces of evidence for Volhard's view that in nephritis the hypertension is of chemical origin, while in essential hypertension it is not (9). Gordon and Levitt (3) recently found that the minimal dose of adrenaline producing a change of the arterial pressure is no less in nephritic hypertension than in essential hypertension or normal subjects.

We have repeated Deicke and Hulse's observations, following their method as closely as possible. To measure the venous pressure, a wide bore needle was introduced into the median basilic vein and connected to a manometer tube and reservoir containing 2% sodium citrate, the arm lay 5-15 cm below the level of the sternum, the patient being recumbent, the meniscus recording venous pressure always showed respiratory oscillations of 2 mm or more. The arterial pressure was measured by the auscultatory method in the other arm. After venous and arterial pressures had reached steady levels, 0.5 c.c. freshly prepared 1:100,000 solution of adrenaline hydrochloride in air-free saline was injected either into the venous pressure needle and washed in with citrate solution, or into a vein of the opposite arm. The resultant changes in arterial pressure were not influenced by the site of injection. The rise of venous pressure was invariably found to be much greater when the adrenaline was injected into the vein from which venous pressures were being recorded (Fig. 1). This difference may be attributed to a direct constrictor action of adrenaline on the veins, for in subjects with a prominent cephalic vein we have seen this vessel disappear in its length for several minutes after injecting 0.005 mg adrenaline into its distal end.

The results of our observations are summarised in Table I. The full response of the arterial pressure to adrenaline seems to consist of a very fleeting rise about 15 seconds, a slightly more prolonged fall about 25 seconds, and a sustained rise beginning about 45 seconds after the injection and lasting about 2 minutes. We have omitted the preliminary transient rise from Table I since it was rarely detected. It may be seen that the changes in arterial pressure were fairly uniform in subjects with normal blood pressures, much more variable and on the whole larger in those with raised pressures, particularly in patients with essential hypertension, some of whom responded with a considerable fall, others with a considerable rise. The

changes in venous pressure summarised in Table I represent the responses to intravenous injection of adrenaline into the arm opposite to that recording venous pressure and thus represent changes in systemic venous pressure. It will be seen that the rises of venous pressure were fairly uniform and essentially normal in both nephritic and essential hypertension. The rise of venous pressure produced by injecting adrenaline into the arm from which the venous pressure was measured is not shown in Table I, but was determined in all our cases and was essentially similar in all 3 groups, averaging 6.4 cm in normal subjects, 5.0 cm in nephritic hypertension and 5.2 cm in essential hypertension.

Our results thus fail to confirm those of Deicke and Hulse. As far as the changes in arterial pressure are concerned, they too observed great



Fig 1 Shows the venous pressures in cm H₂O measured simultaneously in both arms of a normal subject. At the signal R 0.005 mg adrenaline hydrochloride was injected into the needle connected to the venous pressure manometer on the right side and washed into the vein with citrate solution, the venous pressure rose 5 cm on the right and 2 cm on the left. At the signal L a similar injection was made on the left side the venous pressure rose 2 cm on the right and 9 cm on the left. The venous pressures are referred to the manubrium sterni as zero.

variation in the type and magnitude of response among patients belonging clinically to a single type and they seem to have selected as typical of nephritic hypertension a kind of response which we have more often seen in essential hypertension. We are unable to account for the unusually great rise of venous pressure which Deicke and Hulse found in nephritic hypertension, unless in these cases only they injected adrenaline into the arm from which the venous pressure was measured.

These observations have proved of interest in another way. The theory that hypertension is due to hyperadrenalinæmia has recently been revived by Kuré and his co-workers (8) who present new evidence. These workers claim to have detected in arterial but not in venous blood a labile

vaso-constrictor substance which they believe to be adrenaline, the concentration of this substance they estimate to be equivalent to 1 in 2 million adrenaline in normal subjects, 1 in 600,000 in red hypertension and 1 in 1,200,000 in pale hypertension (Volhard's classification) Their results are difficult to reconcile with those of Hulse (6) who was unable to find any constrictor substance in the arterial blood in hypertension, although by his method he claimed he could detect adrenaline in the arterial blood of normal

TABLE I

Shows the changes in arterial and venous pressures and in the colour of the face produced by intravenous injection of 0.005 mg adrenaline hydrochloride

Diagnosis	Age	Sex	Arterial pressure mm Hg		Response to 0.005 mg adrenaline					
					Arterial pressure mm Hg				Rise venous pressure cm H ₂ O	Pallor
			S	D	S	D	S	D		
Normal	29	M	112	80	13	8	4	0	2.4	Yes
Normal	29	M	114	74	5	0	8	2	1.2	Yes
Rheumatoid arthritis	48	F	120	80	6	8	9	0	1.5	—
Gastric ulcer	51	M	114	62	10	6	8	0	2.0	—
Gastric ulcer	58	M	132	78	13	8	9	0	3.3	Yes
Tabes dorsalis	60	M	100	65	8	8	8	0	1.1	Yes
Anæmia (cured)	61	F	136	—	18	—	8	—	3.1	—
Average	—	—	118	73	10	7	8	0	2.1	—
Chronic nephritis*	17	M	166	105	0	0	16	0	2.9	—
" " *	21	M	196	85	18	—	10	—	—	—
" "	36	M	192	112	0	0	21	—	1.8	Yes
" "	36	M	187	136	0	0	7	0	2.0	—
" "	37	F	165	110	5	7	7	0	1.8	Yes
" "	48	F	208	106	0	0	18	12	—	Yes
Average	—	—	186	109	4	1	13	3	2.1	—
Essential hypertension	41	M	220	140	10	14	7	6	2.1	Yes
" "	49	F	196	110	0	0	26	0	3.5	Yes
" "	54	F	216	112	32	15	30	17	—	Yes
" "	58	F	215	115	0	0	10	3	3.4	Yes
" "	61	F	176	96	40	—	10	0	1.8	Yes
" "	64	F	214	120	12	8	7	7	1.2	—
" "	64	F	234	126	22	20	0	0	0.6	Yes
" "	72	M	178	105	0	0	26	6	0.7	Yes
Average	—	—	208	115	14	8	14	5	1.9	—

* These two patients had in addition aortic regurgitation

subjects after intravenous injection of a quantity too small to influence the arterial pressure. Now it is known that in man adrenaline produces constriction not only of the arterioles but also of the minute vessels of the skin (1). The redness of the face that is usual in patients with essential hypertension

can only be reconciled with a coexisting hyperadrenalinæmia by supposing that in them the minute vessels of the skin are relatively insusceptible to adrenaline. Our experiments show that this is not the case.

From Table I it will be seen that in many subjects with normal and raised blood pressure 0.005 mg adrenaline produced pallor of the face. The degree of paling was related to the intensity of the initial redness of the face, and was thus greater in patients with essential hypertension than in normal or nephritic subjects. In the cases where pallor was not recorded, the face was either not inspected or was so pale initially that the absence of further paling seems unimportant. Pallor was observed at about the time the arterial pressure began to change and lasted about 2 minutes. In 2 cases of essential and 1 case of nephritic hypertension with red faces 0.0025 mg adrenaline also produced pallor lasting about 1 minute, in one of these cases with essential hypertension the injection produced no fall and a rise of 10 mm systolic and 0 diastolic from initial levels of 215 and 115 mm Hg respectively. The susceptibility of the minute facial vessels to adrenaline and their ordinarily dilated state in essential and sometimes unconstricted state in nephritic hypertension are facts that we cannot reconcile with the view that the raised blood pressure is due to the presence of abnormally large amounts of adrenaline in the blood.

Cold

Hines and Brown (4, 5) have suggested that essential hypertension consists of two stages, a first in which hypertension is due to a hyper-reactive vasomotor system and a second in which secondary organic changes occur in the vessels. They claim to have discovered in the response of the blood pressure to a cold stimulus, a method of demonstrating a hyper-reactive vasomotor system. Thus they found the following average rises of systolic and diastolic pressure in response to immersion of one hand in water at 4°C: (a) 8.9 mm and 7.5 mm Hg in 40 normal subjects aged 17-50 years, (b) 30.1 and 21.1 mm in 8 subjects with "potential hypertension" aged 19-44 years with normal blood pressures but with a family history of hypertension, (c) 32 and 21 mm in 7 cases of early or labile hypertension, without retinal sclerosis or cardiac enlargement, (d) 38.4 and 32.5 mm in 11 cases of hypertension with retinal sclerosis and enlarged heart, (e) 13.1 and 10.8 mm in 8 patients aged 55-91 with arteriosclerosis but without hypertension.

To test the effect of cold we used a method similar to that of Hines and Brown, one hand of the recumbent subject being immersed to the wrist in water at 4°C for 3 minutes. In each case the subject was quiet, had a steady pulse and blood pressure, felt comfortably warm and had naturally warm hands before the immersion. The rises of blood pressure produced in response to this procedure are summarised in Table II, where we have divided the subjects tested into four groups. It will be seen that

the response was very variable in each group, particularly in the elderly control series and in the patients with essential hypertension, and that the average size of the response was approximately the same in the elderly subjects with normal blood pressure as in those suffering from essential hypertension. In any one subject tested under similar conditions on a number of occasions the size of the response remained fairly constant, thus

TABLE II

Shows the rise of blood pressure (systolic and diastolic, in mm Hg) in response to immersing one hand to the wrist in water at 4°C

Number sub jects	Description	Age in years		Resting blood pressure		Rise of blood pressure to cold	
		Limits	Mean	Limits	Mean	Limits	Mean
7	Control	20 to 37	33	98/60 to 142/85	120/78	0/0 to 15/20	8/6
9	Control	42 to 64	53	108/64 to 142/80	130/76	3/0 to 60/20	22/11
4	Chronic nephritis.	25 to 48	36	145/98 to 196/136	170/109	11/5 to 26/10	17/9
12	Essential hypertension	40 to 66	54	182/92 to 252/138	218/126	2/5 to 50/42	21/13

a woman of 55, suffering from rheumatoid arthritis of 9 years duration and with a normal blood pressure, experienced a rise of systolic pressure which lay between 24 and 32 mm Hg when tested on 7 different occasions, in three other control subjects tested on 2 occasions the variations were no greater. From our observations we would conclude that the rise of blood pressure produced in this test is fairly constant for each individual, that it tends to be larger in old subjects than in young, and that its size seems to be related to the degree of discomfort which the subject experiences but is to a large extent independent of the resting blood pressure. Our series is too small to exclude the possibility that the rise of blood pressure is in general larger in subjects with hypertension than in those of similar age with normal pressures.

In view of the difference between our conclusions and those of Hines and Brown we may add that we see no reason to suppose that our elderly patients with normal blood pressures belong to the class of potential or labile hypertension, they gave no family history of the disease and had attained an age such that a "potential" should have become an actual hypertension.

CONCLUSIONS

1. No evidence has been obtained that patients with chronic nephritic hypertension are abnormally sensitive to adrenaline.

2 Evidence has been provided against the view that essential and nephritic hypertension are due to hyperadrenalinæmia

3 The suggestion that a relatively large rise of blood pressure in response to a cold stimulus is peculiar to potential or developed cases of essential hypertension is unconfirmed

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THE PERIPHERAL RESISTANCE IN PERSISTENT ARTERIAL HYPERTENSION

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IN spite of the attention that it has received from the experimental as well as from the clinical aspect, high blood pressure remains a symptom that is little understood. Although the available evidence suggests that persistently raised arterial pressure in man results from narrowing of the peripheral vessels, the information is in certain respects incomplete, moreover there is little evidence to show whether the vaso-constriction is confined to some organs or affects all, and what is the nature of the abnormal agent which brings it about. A review of previous work reveals that a possible cause of our ignorance is that most workers have studied the circulation as a whole, thereby encountering factors so complex as to defy exact analysis. It seemed possible that useful information might be got from a study of part of the circulation instead of the whole, and since the upper limb is accessible and its circulation relatively well understood, this part has been the subject of the investigations which follow. By restricting enquiry in this way it is impossible that a complete answer should be obtained to some of the questions raised, and while these observations leave undecided the ultimate nature of the agent responsible for high blood pressure, it is hoped that they may help to indicate the direction in which it may be profitable to search.

Material This paper is chiefly concerned with observations on patients with persistent hypertension. In all these patients the systolic pressure was over 160 and the diastolic over 100 mm Hg when the patients were at rest. Most of them had some cardiac enlargement, none had congestive cardiac failure. They have been divided into the following groups —

- (1) Chronic nephritis. These were young adults who had previously suffered from acute nephritis, or who had a considerable and often progressive impairment of renal function with persistent hæmaturia. Signs of retinal arteriosclerosis were present in all cases except one (J C).

* Work undertaken on behalf of the Medical Research Council

(2) Malignant hypertension Two patients who had considerably raised blood pressures and slight impairment of renal function without any history of acute nephritis, but who had albuminuric retinitis with retinal arteriosclerosis

(3) Essential hypertension Patients whose renal function was normal or but slightly impaired, who had no hæmaturia, and whose retinæ did not show the changes characteristic of albuminuric retinitis Signs of retinal arteriosclerosis were present in all except three patients

(4) Coarctation of the aorta In these patients the blood pressure was raised in the arms but normal in the legs, the summit of the femoral pulse was later than that of the radial, and collateral vessels were palpable between the scapulæ Retinal arteriosclerosis was slight or absent

(5) A case thought to be one of basophil adenoma of the pituitary (Cushing's syndrome) who is still alive and is reported fully elsewhere (42)

As controls for these cases, subjects with normal blood pressure were selected from the laboratory staff and from convalescent patients in the wards Many of the older control subjects had some degree of brachial arteriosclerosis, but none were anæmic or febrile

The peripheral resistance in persistent hypertension

A number of determinations have been made of the cardiac output in hypertension, and these have been reviewed recently by Grollman (16) While many of the results have been obtained by methods that are suspect, the more reliable methods have shown that in many cases of persistent hypertension the cardiac output is but slightly greater than normal Thus Liljestrand and Stenstrom (32) using the nitrous oxide method found cardiac outputs of 2.7 to 3.2 litres per square meter of body surface in 3 cases of chronic nephritis Hayasaka (19) using the triple extrapolation method obtained cardiac outputs which averaged 3.2 litres in 14 cases of benign (essential) hypertension, 3.4 litres in 5 cases of malignant hypertension, 2.0 litres in 7 cases of chronic nephritis, and 2.2 litres per square metre in 7 normal adults Blumgart and Weiss (3) found normal circulation times in essential hypertension without cardiac failure There is general agreement that increases in the cardiac output of this order do not account for the abnormally high arterial pressures of the subjects examined, and it is therefore concluded that the factor responsible for persistently raised blood pressure is an increase in the frictional resistance to the flow of blood through the systemic vessels Inspired by the teaching of the older physiologists who stressed the importance of the splanchnic area in the control of blood pressure, many have supposed that high blood pressure is

due primarily to narrowing of the vessels supplying the abdominal viscera * If hypertension were due to narrowing of the vessels in certain areas of the body only, we should expect symptoms of ischaemia to arise from organs lying within these areas. Since such symptoms are uncommon in hypertension, at least in early cases, and occurring, may usually be attributed to localised structural changes in the vessels, it seems probable on clinical grounds that high blood pressure usually results from a cause which affects the circulation as a whole. Information relevant to this question may be obtained by measuring the rate of bloodflow through the forearm, for in hypertension this rate may be expected to be normal if the forearm vessels share in a generalised increase in the peripheral resistance, and increased if the peripheral resistance is more greatly increased elsewhere. Such measurements were made 15 years ago by Hewlett and Zwaluwenburg (22), but their work was done before nephritic and essential hypertension were clearly distinguished and before the desirability of controlling limb temperature was appreciated.

The rate of bloodflow through the forearm. The rate of bloodflow through the forearm has been measured by Hewlett and Zwaluwenburg's method, using the plethysmograph designed by Lewis and Grant (30) and the technique which they described. For these observations the subject lay on a couch in a quiet room at a temperature of 20° to 22°C, the body being lightly covered so that the subject felt comfortably warm. One forearm was enclosed in a plethysmograph and immobilised by sandbags in a water bath maintained at 32°C. After an initial period of 30 minutes or more, the bloodflow through the forearm was determined by recording on a smoked drum the rate of volume change of the contents of the plethysmograph when the venous outflow was obstructed by suddenly inflating a cuff on the upper arm to 60 mm Hg. Measurements were repeated at intervals for at least an hour.

The results of these observations are shown in Table I, the figures for two of the normal subjects being taken from Lewis and Grant's paper. It will be seen that in all the patients with persistent hypertension, the rate of bloodflow varied within the normal limits, though in one case of essential hypertension it was a little high and in another a little low, it is improbable

* In support of this, reference is often made to Jansen, Tams and Achelis (24) who found in the dog that the rise of blood pressure produced by obstructing the iliac arteries was greater and more persistent if the superior mesenteric artery were obstructed previously. They found that binding three limbs in succession to the point of occluding the arteries produced slight and transient rises of pressure in normal and larger and more persistent rises in hypertensive subjects narcotised with veronal and morphia, and argued that this difference showed the inability of the splanchnic circulation in hypertension to accommodate the blood displaced from the limbs. I have been unable to repeat Jansen, Tams and Achelis' observations on men without narcosis because in subjects with high blood pressure binding the thigh sufficiently tightly to empty it of blood is extremely painful. Obstructing both femoral arteries digitally in the groin produced slightly larger rises of blood pressure in patients suffering from nephritic and essential hypertension than in normal subjects but the rises were not significantly different from those produced by pressure on the groins not involving the femoral arteries. I am inclined to think that the responses obtained by Jansen, Tams and Achelis were largely responses to painful stimuli, in animal experiments at least the response to such stimuli is not abolished by light narcosis.

that any special significance attaches to these aberrant results. The average rate of flow is much the same in each group, thus it is 4.5 c.c. per 100 c.c. forearm in 4 subjects with normal pressures, 4.4 c.c. in 3 patients with chronic nephritis, 4.25 c.c. in a patient with malignant hypertension and 4.3 c.c. in 4 patients with essential hypertension.

TABLE I

Shows the bloodflow through the forearm in c.c. per 100 c.c. per min. in subjects with normal and raised blood pressures at rest under comparable environmental conditions

Case	Description	Age and sex	Blood pressure mm Hg		Room temp °C	Bath temp °C	Forearm bloodflow c.c. per 100 c.c. per min
			S	D			
G	Normal	33 M	120	88	22	32	3.2 to 4.2
W.P.	Gastric ulcer	36 M	126	72	21	33	3.1 to 5.5
L	Normal	45 M	120	90	22	32	3.8 to 5.8
A.D.	Diabetes	62 F	125	85	22	32	3.75 to 6.7
L.M.	Chronic nephritis	26 M	175	135	22	32	2.5 to 7.3
H.B.	" "	37 F	160	105	20	32	3.4 to 3.8
M.W.	" "	48 F	214	115	20	32	3.3 to 6.5
W.F.	Malignant hypertension	50 M	230	155	22	32	3.5 to 5.0
K.S.	Essential hypertension	40 F	176	115	22	32	6.5 to 6.8
J.C.	" "	41 M	180	115	20	32	1.7 to 3.0
F.H.	" "	54 F	204	130	21	32	3.7 to 5.4
H.C.	" "	58 F	200	130	20	32	3.1 to 3.4

These determinations show clearly that in the types of persistent hypertension here studied, the resistance to the flow of blood through the forearm vessels is increased. They show further that the increase of peripheral resistance is such that, if generally distributed through the tissues of the body, it is sufficient to account for the raised arterial pressure, for in the forearm the effect of increased resistance balances almost exactly the effect of increased arterial pressure on the rate of bloodflow.

The measurements just described are measurements of bloodflow through muscle and skin, and it is conceivable that an increase in bloodflow through one of these tissues may be balanced by a decrease through the other. This, however, is unlikely for Steele and Kirk (49) measuring skin temperatures at intervals throughout the day, found no material difference between normal subjects and patients with essential hypertension, and such has been my own experience in both nephritic and essential hypertension.

Again Ellis and Weiss (53) using Lewis and Haynal's capsule found the capillary pressure in the skin over the sternum to be normal in essential hypertension. It is thus probable that the bloodflow through the skin is normal in persistent hypertension and therefore, by exclusion, through the muscles also.

Reactive hyperæmia It seemed that some light might be thrown on the nature of the increased peripheral resistance by investigating the action on forearm bloodflow of a dilator agent, and as such the dilatation which succeeds arrest of the circulation (reactive hyperæmia) was chosen, as its

TABLE II

Shows the forearm bloodflow after varying periods of circulatory arrest. The measurements were made at the same sitting as those recorded in Table I which gives other relevant details of the observations.

Case	Description	Blood pressure mm Hg		Forearm bloodflow in c.c. per 100 c.c. per min after circulatory arrest lasting				
		S	D	$\frac{1}{2}$ min	1 min	2 min	5 min	10 min
G	Normal	120	88	—	26.2	48.3	59.8	40.0 to 69.3
W.P.	Gastric ulcer	126	72	12.7	19.4	—	24.0	—
L	Normal	120	90	14.6	16.8	27.0	39.6 to 48.6	37.5 to 49.0
A.D.	Diabetes	125	85	11.7	18.8	—	—	36.5
L.M.	Chronic nephritis	175	135	—	19.6	33.5	37.0	—
H.B.	" "	160	105	11.3	21.0	—	37.5	39.0
M.W.	" "	160	105	10.2	12.7	20.0	35.7	38.5
W.F.	Malignant hypertension	230	155	10.2	11.9	—	31.3	39.5
K.S.	Essential hypertension	176	115	17.8	23.7	—	48.7	62.5
J.C.	" "	180	115	9.6	15.4	30.0	40.0	45.0
F.H.	" "	264	130	13.6	22.5	—	45.0	52.0
H.C.	" "	200	130	—	11.8	14.7	34.3	35.7

mechanism has been fully investigated by Lewis and Grant (30). Determinations of the bloodflow through the forearm after varying periods of circulatory arrest were accordingly made by Lewis and Grant's technique at the same sitting as the determinations of resting bloodflow already described. The circulation to the arm was arrested by inflating to 50 mm Hg above systolic pressure the cuff on the upper arm, and after the requisite interval of circulatory arrest the cuff pressure was abruptly reduced to 60 mm Hg and the inflow curves recorded. After removing this congesting pressure and allowing adequate time for recovery, the observation was repeated with a different period of arrest.

The results of these observations are shown in Table II, the figures for two normal subjects being again taken from Lewis and Grant's paper. It will be seen that, like the resting bloodflow, the rates of bloodflow through the forearm after periods of circulatory arrest lasting $\frac{1}{2}$ to 10 minutes are essentially the same in the subjects with raised and those with normal pressures. This similarity extends also to other details of the response. Thus if the arm of a normal subject and that of a subject with nephritic or essential hypertension are immersed in a bath of water at 32° and the circulation to both arrested for 5 or 10 minutes and released, the reactive flush is similar in intensity and in duration in the two arms. These results are of interest from many points of view. Thus Lewis and Grant concluded that reactive hyperæmia was due to the direct dilator action on the minute vessels of substances released locally from active tissues and normally washed away by the blood stream. If the release of these substances were diminished, or if the vessels responded to them less vigorously, an increased peripheral resistance might be foreseen, but the normal response to circulatory arrest indicates that no such disturbance occurs in persistent hypertension, at least in the forearm. Again the large increase in bloodflow that occurs in subjects with persistent hypertension after long periods of circulatory arrest indicates that the vessels are capable of considerable dilatation. Lastly, the normal rate of bloodflow during reactive hyperæmia suggests that the factor which raises the peripheral resistance in persistent hypertension is one that is stable during circulatory arrest lasting up to 10 minutes, for, if it disappeared during circulatory arrest, the unhampered effect of raised blood pressure would produce abnormally rapid rates of bloodflow.

The viscosity of the blood An increase in the frictional resistance to the flow of blood through the vessels might arise either from vasoconstriction or from increased viscosity of the blood. In acute and chronic nephritis with hypertension Austrian (1) has shown that the viscosity of the blood is usually within the normal limits, or below in cases with considerable anaemia. On the other hand Harris and McLoughlin (18) found that in 40 cases of hypertension, selected at random and therefore presumably mainly cases of essential hypertension, the blood viscosity was raised. In a small series of patients I have determined the viscosity of the blood by means of the rapid velocity viscometer described by Whittaker and Winton (54), who have shown that with this apparatus values for the apparent viscosity of the blood approximate more closely to the values obtained when the isolated limb is used as viscometer than do those with the slow velocity instrument of Hess. 20 c.c. of blood were withdrawn from an arm vein into 0.2 c.c. saturated potassium oxalate to prevent coagulation. The blood was brought to 37° in a water bath and rapidly transferred to an inverted conical flask connected to a capillary tube 46 cm. long and 1.08 mm. internal diameter surrounded by a condenser maintained at 37°. The rate of bloodflow through the tube, when a pressure of 100 mm. Hg was thrown

into the conical flask, was determined and compared with the rate of flow of water under similar conditions. The results are shown in Table III. From this table it may be seen that a patient with chronic nephritis and one with malignant hypertension were both moderately anæmic and had blood viscosities below the normal range. The blood viscosities of the 7 patients with essential hypertension were within the lower normal range. These results indicate that the increased resistance to the flow of blood through the vessels in persistent hypertension is not due to increased blood viscosity.

TABLE III

Shows the viscosity of the blood in subjects with normal and persistently raised blood pressure

Case	Diagnosis	Age and Sex	Blood pressure mm Hg		Blood	
			S	D	Hb %	Viscosity
S M	Thread worms	14 F	130	70	88	4.2
A N	Normal	16 M	130	70	100	4.8
H T	Healed acute nephritis	18 F	130	80	88	5.0
R B	Subacute nephritis	22 M	130	80	94	4.7
I B	Normal	24 M	116	84	108	5.1
G P	Normal	31 M	108	74	110	5.6
L M	Chronic nephritis	26 M	190	140	82	3.7
C V	Malignant hypertension	49 F	230	145	76	3.45
E R	Essential hypertension	51 F	174	100	93	4.2
G C	" "	51 M	218	135	92	3.9
A R	" "	56 F	190	110	105	4.0
J E	" "	62 M	200	100	—	5.0
E N	" "	62 F	236	135	88	4.7
A P	" "	63 F	205	115	102	4.1
W M	" "	70 M	170	105	88	4.1

The effect of removing vaso-constrictor nervous impulses on the bloodflow through the hand

We have seen that there is good reason to suppose that persistent hypertension results from abnormal narrowing of the peripheral vessels which increases the frictional resistance offered to the flow of blood. Such abnormal narrowing may conceivably arise in one of three ways, through the agency of the vasomotor nerves, through the agency of a circulating pressor substance, or through a local change in the vessels themselves. The first

of these possibilities can be tested experimentally. Thus if the abnormal vaso-constriction arises through the agency of the vasomotor nerves, removal of vasomotor nerve impulses from a part should result in a greater bloodflow through this part in subjects with high than in those with normal pressures, for, the abnormal factor now being removed and the vessels of normal and abnormal limb being reduced to the same state, the bloodflow will be dependent entirely on the arterial pressure. On the other hand if the bloodflow through a part, whose vessels are freed from the influence of the nervous system, is no greater in subjects with high than in those with normal pressures, it may be inferred that the abnormal factor narrowing the vessels in hypertension is still present and is not nervous in origin.

It seemed, therefore, that the vasomotor nervous hypothesis of the mechanism of hypertension could be put to the test in the upper limb. The choice lay between two methods, namely, that of Hewlett and Van Zwaluwenberg already described for measuring forearm bloodflow, and Stewart's method of calorimetry applied to the hand (50). Stewart's method measures the rate of heat elimination, which is governed by the rate of bloodflow through the cutaneous vessels, of the hand, it does not give an absolute measure of bloodflow because the blood in passing through the hand is not cooled to calorimeter temperature, as Stewart supposed, but to a slightly higher point (17). But, since we are here concerned with a comparison, this consideration is unimportant. The method has the advantage of giving very consistent results if simple precautions are taken, it has the further advantage of giving an index of bloodflow through the skin of the hand, from which vasoconstrictor nervous impulses can be removed by the simple procedure of raising body temperature (31). The chief nerves supplying the hand are also readily anaesthetised. Hewlett and Van Zwaluwenberg's method has the advantage of giving an absolute measurement of bloodflow, rapid flows can be accurately measured when the part is relatively empty of blood, as in the limb immediately after release of its circulation, but when the limb is initially full of blood, as it would be in the circumstances of the proposed experiments, those who have used the method are agreed that its accuracy is questionable. Another objection is the difficulty of removing the influence of the nervous system from vessels supplying the muscles, of which the forearm largely consists, for the evidence available indicates that this cannot be accomplished by warming the body, and the main nerves are relatively inaccessible to anaesthetisation. For these reasons I decided to use Stewart's method for measuring the heat elimination from the hand, its cutaneous vessels being freed from the influence of vasoconstrictor nervous impulses by warming the body. The procedure was as follows —

Method The observations were carried out in a small quiet room at 21° to 24°C. The subject lay warmly clad on a couch, the head and shoulders being raised. The blood pressure was measured after the subject had been quiet for 10 or 15 minutes. One hand was placed in water at

30°C for 15 minutes and then immersed precisely to the level of the distal carpal bones in a Stewart's calorimeter containing 3 litres of water at 30°C and closed by a lid of spongy rubber perforated to fit the wrist. The calorimeter was stirred at a rate of 90 strokes per minute by a device operated by hand and its temperature read at minute intervals from a mercury thermometer graduated in 1/100°C. A few minutes after immersing the hand in the calorimeter, the other arm was immersed in a bath containing stirred water at 44°C, to raise body temperature. Readings of calorimeter temperature were continued until it reached 32° when the hand was removed and, the other arm still being immersed in hot water, the mouth temperature and blood pressure were measured. The volume of the hand immersed in the calorimeter was then measured, and the rate of cooling of the calorimeter determined. The rate of heat elimination from the hand was calculated as follows: Heat elimination in calories per minute = [Rate of rise of calorimeter temperature + rate of cooling of calorimeter (°C per min)] × [Water content and water equivalent of calorimeter in c c]

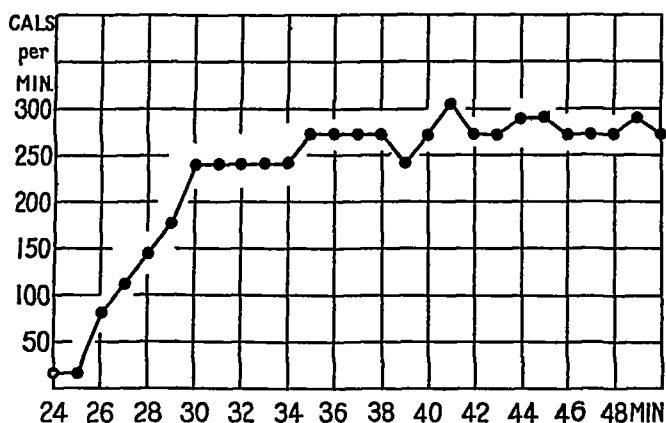


Fig 1 C V, age 49 years, malignant hypertension. Shows the heat elimination (in calories per min) from the right hand (volume = 280 c c) determined by Stewart's method of calorimetry as described in the text. The left forearm was immersed in water at 44° at the 20th minute. The heat elimination rises to a maximum value, which is maintained from the 35th minute onwards. The calorimeter temperature initially 30.5°C, reached 31°C at the 36th minute and was 32° at the 50th. The systolic and diastolic blood pressures were respectively 256 and 154 mm Hg at the beginning, and 230 and 145 mm Hg at the end of the observation. The mouth temperature was 37.6° at the 51st minute.

Results The changes in heat elimination during the course of such an experiment are illustrated by Fig 1, which summarises an observation on a patient suffering from malignant hypertension and which is representative of the events in subjects with normal and raised pressures. In all subjects a few or several minutes after immersing the opposite arm in hot water the rate of heat elimination rose, gradually attaining a maximum value at which it remained with minor fluctuations till the experiment was terminated.

The mouth temperature rose to between 37.5° and 38° and sweating occurred in all subjects. The systolic blood pressure usually fell about 10 mm Hg in normal and 20 mm Hg in hypertensive subjects during the course of the experiment, the falls in diastolic pressures were about half as great. The small fall of blood pressure suggests that such part of the peripheral resistance which is of nervous origin is little altered in the body as a whole when body temperature is raised, though, as will be made clear, it disappears from the skin of the hand. Rein's experiments (47) indicate that changes in vasomotor nervous tone in the skin in response to alterations in environmental temperature are balanced by opposite changes in the gut and perhaps in the muscles.

The rate of heat elimination under ordinary environmental conditions is unimportant, for it is very variable and is chiefly determined through the vasomotor nerves by the state of the body temperature (38) and does not reflect conditions in other vascular territories, it may be said, however, that the rates of heat elimination before immersion of the other arm in hot water were of the same order in normal and hypertensive subjects. The maximum rate of heat elimination in response to warming the body should reflect the rate of bloodflow through the hand from the vessels of which vasomotor nervous tone has been completely removed. By beginning with calorimeter temperatures of 30° to 30.5° , the stage of maximum heat elimination was always reached when the calorimeter had risen to 31° , the figures for the maximum heat elimination given in this paper represent the average rate per minute over the range of calorimeter temperatures 31° to 32°C and are in this, as in other respects, strictly comparable in different subjects.

The method gives consistent results. On separate occasions the maximum heat elimination usually differed by less than 5 per cent in a single subject provided that the blood pressure changed by less than 10 mm Hg. Thus the maximum heat elimination measured on different days in a normal subject was 376 and 362 calories per minute, in a patient with chronic nephritis 310 and 310 calories per minute, and in a patient with essential hypertension 261, 253 and 259 calories per minute. In Table IV are summarised measurements, by the method just described, of maximum heat elimination in 21 subjects with normal blood pressure, 5 patients with chronic nephritis and hypertension, one patient with malignant hypertension, 15 patients with essential hypertension, one patient believed to be a case of basophil adenoma of the pituitary (Cushing's syndrome) and 3 of coarctation of the aorta.

In subjects with normal blood pressures, the maximum heat elimination from the hand is influenced by two factors, namely, the size of the hand and age. In order to allow for differences in the size of hands, the heat eliminations have been expressed in the last column of Table IV as calories per min per cc of hand. Expressed in this way, it will be seen that there is some variation in heat elimination in the four subjects under 30 years old,

TABLE IV

Shows the maximum rate of heat elimination from the hand, determined as described in the text over the range of calorimeter temperatures 31 to 32° C, in subjects with normal and persistently raised blood pressures

Case	Description	Age	Sex	Blood pressure mm Hg		Hand vol c c	Max heat elimination from hand	
				S	D		cals per min	cals per min per c c hand
H S	Normal	17	M	130	80	430	457	1.06
M W	Synovitis	22	F	124	70	290	380	1.30
E B	Normal	24	M	116	84	450	482	1.08
G B	Pyelitis	26	F	126	84	260	330	1.30
G P	Normal	31	M	108	74	370	375	1.00
J S	Gastritis	31	M	124	76	425	369	0.87
P R	Normal	34	M	114	68	400	440	1.10
F B	"	40	F	126	84	280	362	1.29
F M	Gastric ulcer	44	M	124	85	450	320	0.71
W.H.	"	47	M	115	85	440	400	0.90
A.H.	"	51	M	116	68	300	356	1.22
H.H.	Hernia	51	F	116	70	375	288	0.78
A W	Biliary cirrhosis	52	F	146	86	260	333	1.28
R.A	Cholecystitis	54	M	135	86	370	437	1.18
J.H.	Gastric ulcer	56	M	144	77	470	297	0.63
R D	"	57	F	134	88	300	356	1.18
D B	Diabetes	58	F	122	80	320	252	0.79
A M	Carcinoma of stomach	62	M	106	84	350	147	0.42
E B	Gastritis	62	F	126	80	360	246	0.68
A.D	Diabetes	63	F	126	80	290	258	0.89
D	Retinal thrombosis	69	F	118	85	300	248	0.83
L M	Chronic nephritis	26	M	214	145	420	337	0.80
J C	"	35	M	145	108	475	547	1.15
H R	"	36	M	186	135	500	448	0.90
H B	"	37	F	164	124	275	310	1.11
M.W	"	48	F	175	105	260	313	1.20
C V	Malignant hypertension	49	F	230	145	280	273	0.98
K.S	Essential hypertension	40	F	186	115	250	138	0.55
N D	"	41	F	170	100	250	277	1.12
J O	"	42	M	166	116	280	271	0.98
A.A	"	46	F	255	160	300	309	1.03
M C	"	47	F	205	120	270	269	1.0
A K.	"	49	F	216	140	375	285	0.76
G K	"	49	F	200	114	320	366	1.14
A W	"	49	F	228	135	350	245	0.70
J G	"	49	M	195	124	550	281	0.51
F.H.	"	54	F	278	134	350	312	0.89
H C	"	58	F	185	125	375	261	0.70
M.W	"	59	F	176	100	350	341	0.98
E N	"	62	F	236	135	290	200	0.69
F E	"	66	F	216	100	250	269	1.08
F B	Cushing's syndrome	44	F	174	110	325	304	0.94
E B	Coarctation of aorta	21	M	163	100	450	442	1.0
C D	"	39	M	212	115	400	360	0.90
C B	"	58	M	160	80	500	350	0.70

those with small hands having a larger heat elimination per c c hand than those with large hands. It is probable, from these results and from theoretical considerations, that it would have been more accurate to express the results in calories per sq cm of surface area of the hand. A sufficient number of subjects with hands of comparable size and of comparable ages has been examined to make this omission unimportant.

The influence of age is shown in Fig 2 where the maximum heat elimination, in calories per min per c c of hand, is plotted against the age of subjects with normal blood pressure. In young normal subjects the heat elimination

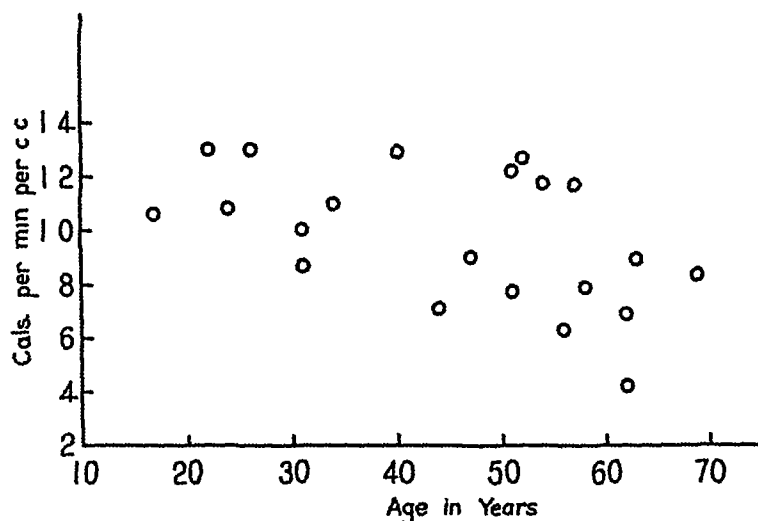


Fig 2 Shows the relationship between the maximum heat elimination, in calories per minute per c c hand and the age of subjects with normal blood pressures

varies from 1.0 to 1.3 calories per c c per minute and although this rate is maintained in some normal subjects up to the age of 58 years, yet there is a tendency for heat elimination to fall gradually as age advances. This tendency is more pronounced in men than in women and particularly in those who use their hands for heavy work. Reduced heat elimination is often associated with signs of sclerosis of the radial and brachial arteries and may be attributed to structural changes in the vessels of the hand which reduce the size of the vascular bed under conditions of vasodilatation. Contemporary observations in this laboratory indicate that sclerotic changes are frequent in the digital arteries over the age of 30 and that intimal thickening and medial fibrosis progress irregularly as age advances. These sclerotic changes seem to have nothing to do with high blood pressure and appear to be largely a function of age and perhaps of injury, to which the vessels of the hand, owing to their exposed situation, are particularly prone.

The extent of the variations in the maximum rate of heat elimination from the hand in subjects with normal blood pressures presents a difficulty in interpreting the significance of the measurements in patients with raised

blood pressures. Nevertheless it may be seen from Fig 3, which compares the two series, that the rate of heat elimination is no higher in subjects with persistently raised pressures than in normal subjects of similar age. In general it may be said that in coarctation of the aorta, chronic nephritis with hypertension and essential hypertension the maximum rate of heat elimination tends to fall within or just below the lower normal range. The same appears to be true of the single cases of malignant hypertension and of Cushing's syndrome, which are shown in Table IV but not in Fig 3. Thus it seems that when vasomotor nervous tone is completely relaxed from the vessels of the hand its bloodflow is not greater in subjects with persistently high than in subjects with normal pressures. This conclusion assumes that

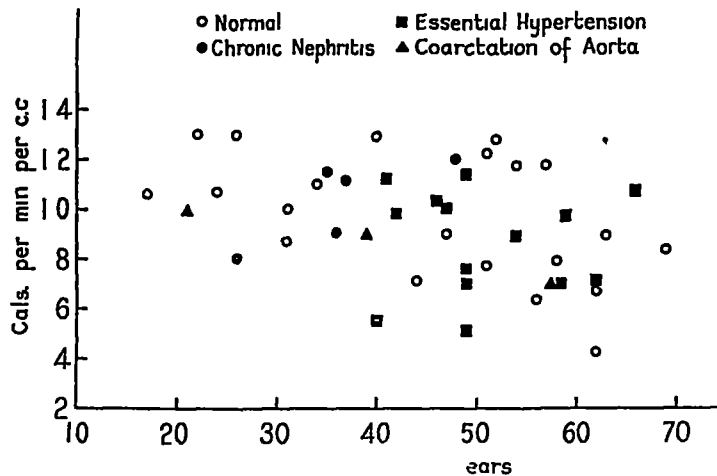


Fig 3 Shows the relationship between the maximum heat elimination, in calories per minute per c c hand, and age of subjects with normal and persistently raised blood pressures

heat elimination is a reliable index of the rate of bloodflow in the hand, and that raising body temperature completely removes vasoconstrictor impulses from the vessels of the hand, before discussing it further, evidence for these two assumptions must be given.

The temperature of the venous blood leaving the hand Since the heat elimination from the hand is determined by the rate of bloodflow and by the heat loss per c c of blood, it is to be anticipated that if in spite of similar heat eliminations the bloodflow were greater in hypertensive than in normal subjects, the venous blood leaving the hand could be warmer in the former than in the latter, we may assume the temperature of the arterial blood to be the same in the two instances for the mouth temperature showed the same range of variation, namely 37.5 to 38°C at the end of the experiment, in both types of individual. In a small series of subjects the temperature of the venous blood leaving the hand was measured during the determination

of maximum heat elimination by introducing a needle thermocouple (17) into a large vein on the back of the wrist, so that the point lay about 1 cm proximal to the line of immersion of the hand, the flow through the vein being unobstructed. Table V shows the temperature of the venous blood recorded at calorimeter temperatures of 31° and 32°C.

TABLE V

Shows the temperature of the venous blood leaving the skin of the hand during the determination of maximum heat elimination over the range of calorimeter temperature 31 to 32°C. The venous temperatures correspond to calorimeter temperatures of 31° and 32°C.

Case	Description	Blood pressure mm Hg		Hand vol c c	Maximum heat elimination		Venous temperature °C	
		S	D		Cals per min	Cals per min per c c hand	Cal at 31°	Cal at 32°
G P	Normal	108	74	370	376	1.01	33.3	34.0
G P	Normal	110	75	370	362	0.98	33.6	34.0
E B	Normal	116	84	450	482	1.08	32.6	33.7
L M	Chronic nephritis	136	103	420	248	0.59	31.2	32.4
H B	"	174	110	275	310	1.14	32.6	34.0
M C	Essential hypertension	196	108	270	248	0.92	32.7	33.6
G K	"	198	115	320	362	1.14	33.2	34.5
A W	"	228	135	350	245	0.70	33.0	33.9
J E	"	190	100	370	258	0.70	32.3	32.8
C D	Coarctation of aorta	212	115	400	360	0.90	33.2	33.9

It will be seen that the venous blood temperature is not higher in subjects with raised than in those with normal pressures, confirming the view that the rate of bloodflow through the hand of the hot subject is not increased in persistent hypertension. In general the higher venous blood temperatures are associated with the larger rates of heat elimination per c c of hand, and the lower temperatures with the smaller rates of heat elimination. This association suggests that the blood is cooled more efficiently when it flows slowly than when it flows rapidly through the hand, a suggestion entirely in harmony with theoretical considerations. It is thus likely that the relationship between bloodflow and heat elimination is not strictly linear, the heat elimination tending to underestimate large as compared with small bloodflows.

The effect of anaesthetising the ulnar nerve. In previous papers evidence has been provided to show that in normal and certain diseased subjects warming the body completely removes constrictor nervous tone from the vessels of the hand, though not always from those of the feet (31, 40). It

seemed possible, however, that if the abnormal factor narrowing the vessels in hypertension were nervous in origin then this fraction of vasomotor nervous tone might be stable and unaffected by warming the body. The assumption that warming the body completely inhibits vasoconstrictor nervous impulses to the vessels of the hand in both normal and hypertensive subjects was therefore tested by comparing the heat elimination in response to warming the body, before and after anaesthetising the ulnar nerve with novocaine at the elbow. For if warming the body does not completely abolish vasoconstrictor impulses, interrupting the nerve supply to a large part of the hand should increase heat elimination. The results are

TABLE VI

Compares the maximum heat elimination from the hand in response to warming the body with and without local anaesthesia of the ulnar nerve at the elbow

Case	Description	Age	Sex	Hand vol c c	Warming body		Warming body and ulnar anaesthesia			
					Blood pressure mm Hg		Max heat elimination, cals per min	Blood pressure mm Hg		Max heat elimination, cals per min
					S	D		S	D	
P R	Normal	34	M	400	114	68	439	122	74	437
F B	Gastritis	62	F	360	124	80	246	112	74	232
L M	Chronic nephritis	26	M	420	214 136	145 103	337 248	164	120	290
K.S	Essential hypertension	40	F	250	186	115	136	162	105	124
M C	"	47	F	270	215 190	124 115	269 257	194	115	268
A W	"	49	F	350	228	135	245	236	135	238

summarised in Table VI. In the two subjects with normal blood pressures the maximum heat eliminations were 1 per cent and 5 per cent less when the ulnar nerve was anaesthetised than when it was not. In the subject with chronic nephritis the results are complicated by the effects of alterations in blood pressure shortly to be discussed, it may be noted, however, that the values for maximum heat elimination and blood pressure after ulnar anaesthetisation were intermediate between the corresponding values obtained without ulnar anaesthetisation. In the three subjects with essential hypertension the maximum heat eliminations with ulnar anaesthesia were respectively 10 per cent, 0 per cent and 2 per cent less than those without anaesthesia. These results show conclusively that in subjects with normal and raised blood pressures warming the body as here described is sufficient completely to remove vasoconstrictor impulses from the cutaneous vessels

of the hand. The general tendency for the heat elimination to be less when the ulnar nerve is anaesthetised than when it is not is consistent with the view previously expressed that the cutaneous vessels of the hand are also influenced by vasodilator impulses which come into play when body temperature is raised (31), the small size of the difference, particularly in view of the tendency for the blood pressure to be lower after nerve anaesthetisation, shows that these vasodilator impulses are ordinarily unimportant.

The effect on maximum heat elimination of variations in the arterial pressure. The effect on maximum heat elimination of increase in blood pressure, the vessels of the hand remaining unchanged, was deliberately tested in a patient having a large arteriovenous fistula of a common femoral artery previously investigated and described by Lewis and Drury (29).

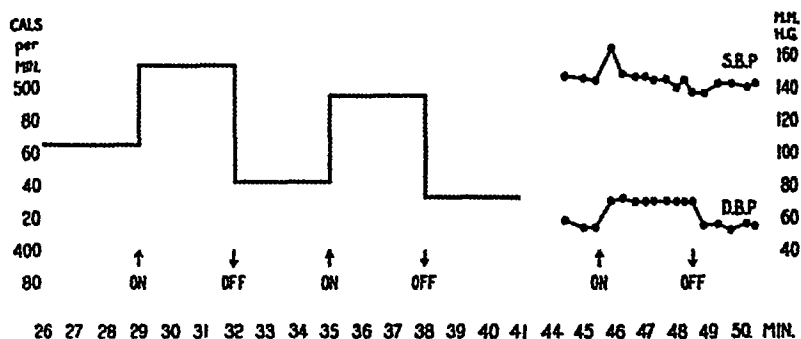


Fig 4 A.L., age 46 years, arteriovenous fistula of right femoral vessels of 18 years duration. The right forearm was immersed in water at 44° throughout the observation. The maximum heat elimination from the left hand (in calories per minute) and the systolic (S.B.P.) and diastolic (D.B.P.) arterial pressures are shown. At "on" the right femoral artery was obliterated by digital pressure, thus cutting the fistula out of the circulation, at "off" the artery was released.

Lewis and Drury showed that in this patient compressing the artery proximal to the fistula produced a considerable rise of blood pressure and increase in bloodflow to the limb, in the circumstances of their experiments it was possible, however, that the rise of blood pressure produced an increase in bloodflow indirectly through the vasomotor nerves activated by stimulation of the carotid sinus and depressor mechanisms. If, however, vasomotor nervous tone were previously abolished from the vessels of the hand by raising body temperature, any increase in heat elimination that resulted from compressing the aneurysm would be due to a passive effect of raised arterial pressure on the bloodflow through the hand. The observation was therefore repeated under these conditions, the heat elimination being determined from one hand, the other forearm being immersed in hot water to raise body temperature. The results are shown in Fig 4, in which the heat elimination from the hand is averaged for periods each of three minutes. In the first, third and fifth of these periods, the patient was undisturbed.

and the gradual decline of heat elimination as calorimeter approached nearer to blood temperature may be noted. Throughout the second and fourth periods the arteriovenous fistula was out of the circulation by compressing digitally the femoral artery proximal to the lesion, it will be seen that in both of these periods the heat elimination was considerably greater than during the preceding and succeeding periods when the fistula was open. After the fifth period in the chart, the hand was removed from the calorimeter and the blood pressure determined before, during and after excluding the aneurysm for 3 minutes, the other conditions remaining unchanged. To sum up this observation we may say that the maximal heat elimination averaged 446 calories per minute under conditions when systolic and diastolic blood pressures averaged 143 and 55 mm Hg, and 503 calories per minute when the pressures averaged 147 and 70 mm Hg.

The effects of considerable variations in blood pressure on the maximum heat elimination were also observed by chance in the patient L M suffering from chronic nephritis who was alluded to when the effects of ulnar anaesthesia were considered. In L M injection of novocaine around the ulnar nerve, and as a subcutaneous button preparatory to introducing the intravenous needle thermocouple, produced on each occasion a sensation of faintness and a fall of blood pressure lasting over an hour, determinations of maximum heat elimination were made during the period of low blood pressure (Tables V and VI). Before and several hours after novocaine injection the blood pressure was at its usual high level for this subject. Cotton and Lewis's observations (5) suggest that in fainting the fall of blood pressure is due to vagal effects on the heart and to changes in vascular tone of nervous origin, and it is probable from the circumstances in which it developed that the fall of blood pressure produced in L M by novocaine injection was of similar origin. It is to be anticipated, therefore, that in the determinations of maximum heat elimination on this subject the vessels of the hand, freed from the influence of the nervous system by warming the body, were in the same state when the blood pressure was high and when it was low and that the changes in heat elimination were the passive effects of the alterations in blood pressure. This is supported by Fig 5 which shows the relationship between the heat elimination and the diastolic pressure in L M and in the patient with arteriovenous fistula already described, for it will be seen that equal increments of diastolic arterial pressure are associated with rather similar increments of heat elimination in the two subjects.

This figure indicates the order of change in heat elimination that may be expected from simple variation in arterial pressure. In the patient with arteriovenous fistula the maximum heat elimination was within the normal limits at 118 calories per c c per minute when the arterial pressure was at its usual level. A rise of 15 mm Hg in diastolic pressure raised the heat elimination to 133 calories per c c per minute, a value a little greater than has been found in any other subject. It is evident, therefore, that if the

vascular narrowing in the hand were purely nervous in origin in hypertension, then we might anticipate finding abnormally high heat elimination. In the case of chronic nephritis when the diastolic pressure had fallen to 100 mm Hg the bloodflow through the hand, from which vasoconstrictor tone had been removed, was only about half as great as in comparable normal subjects, for the maximum heat elimination was only 0.59 calories per c.c. per minute, the normal range at this age being 1 to 1.3. Since the resistance offered by the vessels is measured by the ratio between blood pressure and bloodflow, it may be said that in the hand of L.M. the vascular resistance of non-nervous origin was at least twice as great as in comparable normal subjects.

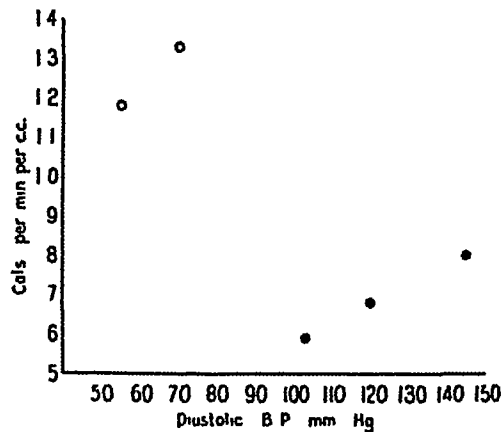


Fig. 5 Shows the relationship between maximum heat elimination, in calories per minute per c.c. hand, and diastolic arterial pressure in the patient with arterio venous fistula (circles) (see Fig. 4) and in L.M., age 26, suffering from chronic nephritis (discs). In the case of L.M. the upper right point summarises a determination of maximum heat elimination made in the ordinary way on 17.5.35, the middle point a determination after anaesthetising the ulnar nerve on 1.6.35, and the lower left point a determination after introducing a needle thermocouple into a vein at the wrist on 4.6.35.

Discussion of results Having now gained some idea of the reliability and significance of the determinations of maximum heat elimination from the hand, we may return to discuss the inferences which may be drawn from the results in patients with persistent hypertension. There can now be no reasonable doubt that in all the types of persistent hypertension here investigated, the vessels of the hand continue to present an abnormally high resistance to the flow of blood after they have been freed from the influence of the nervous system. This narrowing of the vessels of non-nervous origin in persistent hypertension is sufficient to balance or slightly to outweigh the effect of raised blood pressure on bloodflow, it is therefore of an order such that if affecting the vessels generally it would by itself account for the rise of arterial pressure found. The evidence here presented is thus not only entirely consistent with, but seems to provide definite evidence for, the view

that the abnormal agent narrowing the vessels in hypertension is not nervous in origin

Although there is vascular narrowing of non-nervous origin in the hand in hypertension, it might be considered as an effect rather than the cause of raised blood pressure, to be more specific, the vascular narrowing might be regarded as an accentuation, due to long continued high blood pressure, of the presumably sclerotic changes which occur in subjects with normal blood pressure as they grow old. In chronic nephritis the relative youth of the patients is strongly against this alternative explanation. Moreover, there is no relationship in chronic nephritis between the duration of hypertension and the extent of vascular narrowing. As indicated by the relationship between diastolic pressure and heat elimination, the vascular narrowing was of greater extent in H B, aged 36, in whom the duration of hypertension was known to be less than 1 year, than in M W, aged 48, in whom hypertension was known to have been present for at least 8 years. Again, L M was observed continuously over 7 months when the systolic and diastolic blood pressures remained ordinarily over 190 and 140 mm Hg, the heat eliminations from the hand were, for equal blood pressures, similar at the beginning and end of this period. In chronic nephritis therefore the evidence indicates that the reduction in calibre of the vessels of the hand is not an effect of hypertension, but probably represents its cause.

In essential hypertension we are on less certain ground because these patients have reached ages at which changes occur in the vessels of the hand in normal subjects, and because in most cases the duration of the hypertension is unknown. Nevertheless it is unlikely in these subjects that the degree of vascular narrowing can be explained as an effect of hypertension. Thus in two patients (H C and E E) the heat elimination was unchanged after 16 months. If the vascular narrowing in the hand is an effect and not the cause of hypertension, then it should be possible to obtain early cases before the effect has developed. Nine of the patients shown in Table IV and Fig 3 were under 50 years of age, but in none were the maximum heat eliminations above the normal range. More conclusive are the following two cases which, having been seen at an unusually early age, are summarised separately in Table VII. The cases were briefly as follows —

H M, a clerk, aged 22 complained of palpitations and wind after heavy meals, and of occasional dizziness on climbing stairs. His doctor found raised blood pressure. The patient was of normal appearance except for highly coloured face and hands. There were no physical signs of cardiac enlargement or of radial or retinal arteriosclerosis. There were no signs of coarctation of the aorta. The haemoglobin content of the blood was 102 per cent. The urine was normal.

C G, a butcher, aged 32, had repeated nose bleeding for 3 days and consulted his doctor who found the systolic and diastolic blood pressures to be 180 and 110 mm. Hg, respectively. The patient, who had no other complaints, was thick set and had unusually highly coloured face and hands. Clinically, the heart was not enlarged and the radial and retinal arteries were normal. There were no signs of coarctation of the aorta. The urine was normal. The haemoglobin content of the blood was 96 per cent (Haldane scale).

TABLE VII

Shows the maximum heat elimination estimated in the preceding two patients, with the blood pressure before and after warming the body

Case	Age	Sex	Blood pressure mm Hg				Hand vol c c	Max heat elimination	
			Beginning		End			cals per min	cals per min per c c hand
H M	22	M	166	105	154	96	500	416	0.83
C G	32	M	155	100	148	90	420	377	0.90

In both these patients, despite their early age and the complete absence of any signs of vascular sclerosis, the maximum heat elimination was at or below the lower limit of the normal range. In their case it can only be supposed that the increased vascular resistance in the hand represents the effect of the non-nervous agent responsible for the hypertension.

In so far as it is possible to apply to the circulation as a whole conclusions drawn from one vascular area, these results strongly suggest that in chronic nephritis and essential hypertension probably also in malignant hypertension and coarctation of the aorta, high blood pressure is due to vasoconstriction of non-nervous origin. It is, however, to be pointed out that the investigation of other vascular territories is desirable.

The part played by the vasomotor nerves in hypertension

It is generally agreed that in chronic nephritis the hypertension is chemical and not nervous in origin, for in this condition it is probable on clinical (51) and experimental grounds (11) that the high blood pressure is secondary to the renal lesion, and Page (36, 37) has recently produced evidence to show that the renal nerves play no essential part in its production. Essential hypertension is generally considered to be of different origin, and although Volhard (51) considers that it may result from a local abnormality of the vessels, it is usually ascribed to overaction of the vasoconstrictor nerves. In the case of chronic nephritis, therefore, the results obtained here agree with current views, but in essential hypertension they differ, and the evidence for overaction of the vasomotor nerves in this condition must be considered.

The evidence for the nervous theory of essential hypertension is merely that the behaviour of the blood pressure is in many respects compatible with such an origin. In the first place, Kohn (27) has stressed the abnormal variability of the blood pressure in this condition and supporting data will be found in Mueller and Brown's (33) paper. This abnormal variability provides no real evidence for the nervous theory even if we grant, what is not proved, that these changes in blood pressure are due to changes in vascular tone of nervous origin. The responses of the blood pressure to pressor and

depressor chemical agents such as adrenaline and histamine is approximately proportional to the subject's initial level of blood pressure (12, 41, 42), and it is not at all clear, when this allowance is made, that the spontaneous variation in essential hypertension is abnormally great. In the second place Hines and Brown (23) suppose that the unusually great rise of blood pressure produced by a cold stimulus in patients with essential hypertension indicates a hyper-reactive vasomotor centre, in a previous paper it has been pointed out that an unusually large response to a cold stimulus is neither invariable in, nor peculiar to, patients with raised blood pressure (41). Finally

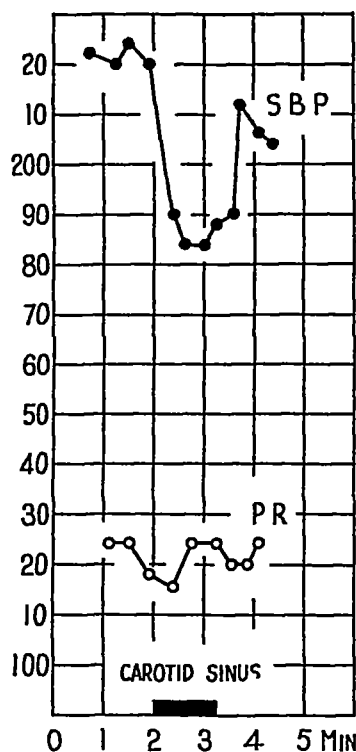


Fig 6 M W, chronic nephritis aged 48 years. 1.3 mg atropine sulphate was injected intravenously 2 minutes before the observation, the pulse rate previously being 76 beats per minute. The figure shows the effect on systolic blood pressure (S.B.P.) and pulse rate (P.R.) of firm digital pressure on the right carotid sinus for 1½ minutes.

the argument is used that section of the splanchnic nerves and removal of the lumbar sympathetic chains produces a fall in blood pressure and amelioration of symptoms in essential and malignant hypertension (6), the significance of such falls of blood pressure as occur is in doubt until we know the effects of similar operations in subjects with normal blood pressures.

All that is indicated by such evidence is that the vasomotor nerves remain active in hypertension. Of this we have further knowledge. Hering (20)

has pointed out that the large fall of blood pressure produced in nephritic and essential hypertension by compressing the carotid sinus, represents a corresponding decrease of vasomotor nervous tone, this conclusion is more legitimate if the effect on the heart is first eliminated by atropine (Fig 6) The falls of blood pressure produced in a patient with chronic nephritis by novocaine injection, have been attributed to changes in vasomotor nervous tone and cardiac output (page 225)

There is thus little doubt that vasoconstriction of nervous origin does constitute a considerable fraction of the peripheral resistance in persistent hypertension, as it does in normal subjects, the contention here is that it does not constitute the abnormal factor responsible for the raised arterial pressure This view is in harmony with the conclusion previously reached that in nephritic and essential hypertension the carotid sinus mechanism remains active (42), for this mechanism, according to recent work from Heyman's laboratory (2), acts as an inhibitor of sympathetic vasoconstrictor activity

The nature of the abnormal agent in persistent hypertension

The chief importance of the observations described here is that by providing evidence against the nervous theory they narrow the field of enquiry as to the nature of the abnormal agent in persistent hypertension On this basis we may consider briefly the possible mechanism of persistent hypertension in the various morbid states in which it occurs

In coarctation of the aorta, the blood pressure is raised in the arm and normal in the leg, the bloodflow being normal in both extremities as Lewis's Tables show (28) The raised peripheral resistance in the upper part of the body, which is to be inferred from the association of normal bloodflow with hypertension, must therefore be due to an agent which does not affect the lower half A chemical abnormality of the blood is clearly out of the question and it was anticipated in this condition that the vascular narrowing would be found to be of nervous origin, although no appropriate reflex nervous mechanism is known which would produce increased vascular tone restricted to the upper half of the body The experiments here described are opposed to the nervous hypothesis, and by exclusion we must attribute vascular narrowing in the upper limb to a local change in its vessels Coarctation of the aorta is a congenital affection, the chief features of which are the arrangements securing a supply of blood in apparently normal quantity to the body below the aortic obstruction, these arrangements are firstly the enlargement of collateral vessels connecting the aorta above and below the obstruction, and secondly narrowing of the vessels supplying the tissues above the obstruction as exemplified by the upper limb The development of collateral vessels appears to be determined by local conditions of blood supply and demand and to be independent of the nervous system (13, 34), if such an explanation is found sufficient for this aspect of coarctation, it does not seem unreasonable to apply it also to the vascular narrowing in the

upper limb A suggestion that the vascular narrowing in the upper limb in coarctation represents something in the nature of lessened growth rather than of excessive contraction arises from the observations of Graybiel, Allen and White (15) who found no muscular hypertrophy in the small arteries of the upper limb in this condition, in contrast to the hypertrophy which has been described in the conditions next to be discussed

Chronic nephritis and essential hypertension are clinically distinct conditions, malignant hypertension occupies an intermediate position and is variously thought to be a form of chronic nephritis (48) and of essential hypertension (51) It is clear that hypertension may result from different agents in these several conditions, but with this reservation they may be discussed together here since they have many features in common * In all three conditions the small arteries of kidney, spleen, pancreas and brain usually show thickening of their inner coats which varies in severity (and in histological type in the kidney) in the several conditions (7, 9, 10, 52) Although such changes must increase the resistance which the affected vessels offer to the flow of blood, it is generally agreed that they are not the direct cause of hypertension since they are usually absent in the large vascular territories of gut, muscle and skin, and even in the kidney, their commonest site, they may be minimal in certain cases of essential hypertension (9) and absent in chronic nephritis with hypertension (e g, Case 4 of Branch and Linder (4)) Histological constitutes the strongest evidence that hypertension is not the simple consequence of structural changes in the vessels, in agreement are the sizes of the depressor response to histamine (42) and of the vasodilatation after circulatory arrest, both of which indicate the ability of the vessels to dilate in hypertension Another structural change is said to occur in the smaller arteries in these diseases, namely, hypertrophy of the middle muscular coat, † unlike the intimal, the medial change appears to be diffusely distributed in the body (8), and recent observations indicate that it corresponds approximately in degree with the height of the diastolic

* Alleged differences in response between these two forms of hypertension to small quantities of adrenaline and to stimulation of the carotid sinus mechanism have been examined in previous papers and unconfirmed (41, 42) Raab (46) alleged that patients suffering from essential hypertension respond with a large fall of blood pressure to overbreathing, while patients with nephritic hypertension do not neither Raab's own results, those of Proger and Ayman (45), nor those which Dr Kissin and I obtained in 8 subjects with essential hypertension and 5 subjects with chronic nephritis support this view depressor responses being found irregularly amongst both clinical types (unpublished observations) The only difference which I have observed between the hypertension in patients suffering from essential hypertension and those suffering from chronic nephritis, has been the high systolic relative to the diastolic pressure in the former It may be suggested that this difference is due to a difference in the degree of sclerosis of the large vessels in the two types of hypertension consequent on their different age incidence, a similar rise of systolic relative to diastolic pressure may be seen in elderly subjects with normal blood pressures (see Table I of previous paper (42))

† Although histologists generally are agreed on this point their evidence cannot be accepted without question Thickening of the vascular wall relative to the lumen might occur not only from hypertrophy but from vaso-constriction As we have seen there is every reason to suppose that the arteries in hypertensive subjects are abnormally constricted during life, if they remain so after death, vessels with a given internal diameter would actually represent larger vessels in hypertensive than in normal subjects

pressure (25) This muscular hypertrophy may be explained on conventional lines as a response to increased work, the smaller arteries in these forms of hypertension being ordinarily contracted more strongly than in normal subjects The evidence supplied in this paper suggests that this abnormal contraction is not nervous in origin, it is therefore presumably chemical

In a recent paper (39) it has been shown that introduction of as much as 600 c c blood from patients with essential hypertension into other human subjects produces no greater rise of blood pressure than does a similar quantity of normal blood, it therefore seems unlikely that essential hypertension results from an abnormal blood content of vaso-active bodies In nephritic and malignant hypertension no abnormal pressor or depressor substance has yet been demonstrated in the blood, but the methods used are more open to criticism (*see* previous paper (39)) While we cannot on negative evidence alone finally exclude an abnormality of the circulating blood, it seems possible that in these conditions high blood pressure results from some local abnormality of the vessels themselves or of the tissues surrounding them If a local vascular change underlies hypertension, it is probably one that is yet unrecognised or imperfectly understood, such as the local excess of a constrictor or deficiency of a dilator substance It is also possible that the actual agent producing vasoconstriction may differ in the various clinical conditions

Any comprehensive theory of the mechanism of essential, malignant, and chronic nephritic hypertension must account not only for the raised pressure but for the intimal lesions in the smaller arteries The generally accepted view that such lesions are due to damage of the vessels by the abnormally high pressure is scarcely justified, for as Hering (21) and Fahr (8) have pointed out this view fails to explain why these lesions are confined to certain well defined vascular territories, it is also difficult to reconcile this view with the failure of similar lesions to develop in experimental animals in which the blood pressure has been raised over very long periods as a consequence of excision of the carotid sinus and depressor nerves (26, 34) It seems possible that the presumably chemical abnormality which leads to vasoconstriction in these conditions may also play some part in the genesis of the intimal thickening in the smaller arteries which so often determines the course of the disease

SUMMARY

1 Under similar environmental conditions the rate of bloodflow through the forearm is the same in subjects with essential hypertension, malignant hypertension, and chronic nephritis with hypertension as in subjects with normal blood pressures The resistance offered by the vessels of the forearm is increased in these conditions owing to vasoconstriction, the blood viscosity being normal or less than normal The increased vascular resistance is of an order such that, if generally distributed throughout the body, it would account for the levels of arterial pressure observed

2 After periods of circulatory arrest lasting up to 10 minutes, the rate of bloodflow through the forearm increases to the same extent in subjects with persistent hypertension as in normal subjects

3 Using Stewart's method of calorimetry, the rates of bloodflow through the cutaneous vessels of the hands of normal and hypertensive subjects have been compared, after completely inhibiting vasoconstrictor nerve impulses to these vessels by warming the body It is shown that in these circumstances (a) the rate of bloodflow declines in subjects with normal blood pressures as age advances, a decline attributed to sclerotic changes in the vessels of the hand, (b) in the various types of persistent hypertension the rate of bloodflow is never greater, but is sometimes less, than its value in normal subjects of similar age

5 It is concluded therefore that in chronic nephritis and essential hypertension (and probably in the other types of persistent hypertension studied) the abnormal agent narrowing the vessels is not nervous Its probable nature in the several diseases is discussed

Subsequent note

Since this paper was written, very similar work has been published by Prinzmetal and Wilson (43) on the distribution and nature of the increased resistance in persistent hypertension The methods they used are very similar to those here employed, except that when investigating the role of the vasomotor nerves, they measured the rate of bloodflow through the forearm plethysmographically when body temperature was raised by immersing the other arm in hot water and in some subjects when the upper dorsal sympathetic ganglia were injected with novocaine In essential, malignant, and chronic nephritic hypertension they conclude that the abnormal agent narrowing the vessels is not nervous in origin, in these diseases therefore the similar conclusions reached by two sets of independent workers using different methods and investigating different vascular territories makes the case against the nervous hypothesis very strong In the case of coarctation of the aorta our conclusions differ, for Prinzmetal and Wilson conclude that in this condition the increased vascular resistance in the arm is nervous in origin The solution of this difference must be left for future work It may be said, however, that the interpretation I have put on my own results is strictly relevant to the hand alone A large part of the bloodflow through the hand is carried by the arteriolo-venous anastomoses which, as Grant and Bland (14) have shown, are absent at birth, and it is possible that in this congenital affection the lessened vascular growth, which I have hinted may explain the high vascular resistance in the upper limb, is limited to these vessels It may be pointed out that

these remarks apply only to coarctation, they do not apply to essential, malignant, and chronic nephritic hypertension which are not congenital. It may also be said that although the unusually large bloodflows through the forearm, which Prinzmetal and Wilson found in coarctation when body temperature was raised, provide suggestive evidence for the nervous theory, the evidence is not final, for in coarctation circumstances did not permit them to anaesthetise the sympathetic ganglia, a procedure which in normal subjects and subjects with nephritic and essential hypertension produced bloodflows only half as great as those in response to warming the body.

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PAIN AS AN EARLY SYMPTOM OF ARTERIAL EMBOLISM AND ITS CAUSATION

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*The observations herein contained formed the basis of Memorial Lectures to
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Preliminary considerations

THIS paper is especially a study of the pain that is so frequent and so often distressing among the initial symptoms of embolism of main arteries. The pain has been attributed at least in large part, by Welch (55), Odermatt (53), Danzis (15) and many others to the immediate and direct influence of the embolus upon the arterial wall. That a clot, carried onwards until it jams where the artery narrows, causes pain either by its impact or by its stretching of the vessel wall is a view that I have never regarded favourably. For since clot has a similar specific gravity to blood, the momentum of a clot cannot differ materially from that of an equal volume of this fluid, and since clots detached from the heart are usually soft in consistency, and mould themselves to the vessel in which they lodge, it is not very evident why the vessel wall should become stretched very appreciably. When an artery is occluded by digital compression, the walls on the proximal side of the obstruction are thrown into a slightly greater average tension, but such occlusion never gives rise to pain, and there is no evidence that even more considerable distension of the artery than can occur in these circumstances will cause pain.

Throughout the records of published cases of embolism of the limbs runs the repeated and definite inference, or the actual statement, that the instant of embolism is marked by the onset of pain. Embolism is a sudden happening, the patient complains of pain that comes suddenly, and when examined, it matters not how soon afterwards, presents obvious signs that the circulation to the painful limb has been lost. So the conclusion is reached that pain follows embolism as it follows a blow, on the instant. Familiarity with the records shows that there is insufficient evidence for

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this conclusion, which has never been brought beyond the stage of assumption. No case has been recorded in which the pulse has been observed suddenly to vanish at the instant the patient cries out in pain, the argument is really circular, for while the pain is considered to be the immediate result of embolism, the timing of that embolism itself relies on the onset of pain. A fact which has probably contributed to the fallacy is that the patient often describes the first symptom as a sudden severe pain, for this would seem to require for its interpretation some sudden physical event. Most if not all pains may be said to begin suddenly, what the patient really means is that the pain quickly becomes severe. But when without expectation human beings are seized with pain, which grows to a serious culmination and lasts, they are exceedingly apt as time passes to forget all but the pain at the intensity that brings them misery. The statements made by patients of the way in which pain begins are highly unreliable, these always require to be tested by critical interrogation and are most to be trusted when the event is repeated after the patient's close attention has been drawn to the significant points. The history of onset with sudden severe pain, though common in embolism, should not be allowed to carry great weight, probably it is often, possibly it is always, less accurate than the history of pain gradually increasing until it becomes severe, or of an onset with other symptoms.

Unless we are in a position actually to time the lodgment of the embolus, and this can very rarely be done, we cannot determine the interval elapsing between the embolism and the symptoms to which it gives rise. But, in the case of the limb, much of the relevant information can be obtained accurately by deliberately arresting its circulation. The symptoms so produced have been studied in detail by Pickering, Rothschild and myself from the standpoint of paralysis and from the standpoint of pain (51, 52). The relevant facts elicited may be stated briefly.

Firstly in regard to paralysis, this never begins at the moment the circulation is arrested, but only after an interval of about 15 minutes. Here it is important to emphasise that we are discussing ischæmia of the limb. Ischæmia of the spinal cord, resulting from occlusion of the aorta as high as the renal arteries, leads to paraplegia almost at once (Schiffer (54), Herter (49)), and not after the long delay required to paralyse the peripheral nerves. Paralysis due to ischæmia of a limb starts at the very end of the limb in a defective sense of touch, which spreads up the limb and is followed later by similar centripetal loss of other forms of sensation. Loss of motor function shows a like march and is almost simultaneous with loss of touch sense. The point requiring stress is that the development and spread of anæsthesia in an arm to the elbow, or in a leg to the knee, with the associated motor weakness, occurs only after the lapse of periods of the order of a half hour. When a patient suffering from embolism is found to present anæsthesia of this extent, it is quite certain that the embolus has occurred at least a half hour previously. The fact is most relevant to many case histories of embolism, for if a patient's statement is to be accepted that, at the time

pain was first experienced, extensive numbness or motor paralysis was noted simultaneously, it becomes quite certain that the plugging long preceded the onset of pain. Now histories of this type are frequent and, as will be exemplified later, it may even be stated or known that pain comes definitely after paralysis. In considering the time relations of the onset of pain to numbness or motor weakness, it is to be recognised that the last two symptoms are apt to be long overlooked, the fact is really a familiar one, being well illustrated by a leg that has "gone to sleep," for usually the limb is recognised to be insensitive and weak only when it comes to be moved.

Secondly in regard to pain, when the circulation to a limb is completely arrested experimentally, the time at which pain appears varies very greatly. If the limb is doing work, pain can come quickly, namely, within a half minute or a little more, and will often rise quickly to a pitch of very great severity. But if the limb is kept at absolute rest, more than half an hour may elapse with little more discomfort than slight aching of the part. According to circumstance pain may come after a short delay or may be delayed for intermediate or for very long periods of time. Thus, it happens that pain may come long before there are paralytic symptoms, or it may be delayed until after these symptoms are distinct. As will appear later, similar variations are found in the order of symptoms arising out of embolic closure of limb arteries.

These considerations help to keep the mind alert to construe the symptoms and signs in clinical cases aright, and are appropriate preliminaries to the following enquiry, which leads to the conclusion that embolism does not give rise to pain as an initial symptom by affecting the vessel wall locally, but by depriving distal tissues of their proper blood supply. Evidence will be collected to show that characteristically the pain of embolism is not at the site of embolism but is beyond it, further evidence will be presented that pain does not necessarily mark the instant of embolism and that other symptoms often come first.

It will be manifest that these two chief pieces of evidence are strongly opposed to the view of a local origin of embolic pain and favour the theory that it arises as an effect of ischæmia, other evidences that will be discussed point in the same direction.

MAIN OBSERVATIONS

It has been stated, not infrequently, that the pain of embolism of the limbs is felt in the region of the clot. Such, however, has not been my own clinical experience, speaking of non-infective clots I have found that the pain is usually referred to a point distal, and often much distal, to the clot. Pain is sometimes felt in a region as high as the clot, and there is no reason, on the basis of the ischæmic view of its production, why it should not, thus when a clot obstructs the profunda femoris it blocks a vessel supplying muscle and other tissues at that level. It is true that when a clot lies for many hours or several days in an artery, the region of the clot becomes tender,

and pain may occur in it spontaneously or be provoked from it by manipulation. These symptoms, often associated with superficial signs of inflammatory reaction, are especially frequent in the case of the emboli of subacute infective endocarditis. But it is not with consecutive symptoms, it is with the pain as an initial symptom of embolism that we are here concerned. That pain from non-infective emboli of aorta or main vessels of the limbs is usually located beyond the obstruction can be substantiated by past records. Information gathered from these records as to the location of the pain, and other points relevant to the discussion of its ischæmic origin are briefly reviewed in the following paragraphs. Of the very many cases that have been reported, we shall confine ourselves almost strictly to those in which the position of the clot has been determined at operation or after death.

Obstruction of the aorta at its bifurcation

If there are differences between the symptoms arising out of embolism and thrombosis of the aorta, they are unknown, the symptoms are the same whether clots found at the bifurcation may be supposed to have formed *in situ* or to have been dislodged from the left auricle or ventricle. Of cases in which the site of obstruction has been proved at autopsy or at operation a sufficient number has been recorded to enable us to describe the associated pain. The characteristic pain is not abdominal but occurs in the lower limbs. It is usually described as severe and, without closer localisation, as occurring in the legs, it may extend from hip to foot, it may be in one calf and foot (Lundblad (7) Case 1), it may be cramp-like, it is almost always described in association with sensory or motor paralysis and with clear signs of loss of circulation to the legs, though the order in which these symptoms appear is rarely recorded. The case described by Boccherini (10) is instructive. Here a tearing cramp-like pain was experienced in the left leg of an elderly cardiac subject, and was soon followed by pain in the right leg. The legs became cool and discoloured. The right limb recovered, but motor and sensory paralysis were established in the left leg. The clot was found in the bifurcation of the aorta, completely blocking the left but not the right iliac artery. The pain, though experienced in both legs, occurred chiefly in that to which the flow of blood was mainly hindered.

Occasionally there may be a preliminary pain in the loins (as in Drevermann's case (3)) or in the abdomen (as in cases of my own) and associated with melæna (Gamble (4, Case 2)), or in the back and associated with hæmaturia (as in a case of my own), followed in each case by pain in the lower limbs. Such preliminary pain is to be ascribed to early involvement of lumbar arteries, mesenteric artery, or renal artery, by separate clot, or by the main clot before it finds its final lodgment at the bifurcation.

While pain is usually given the most prominent place in the symptomatology, it is clear from cases of Malbranc (8), Barié and Halbron (1), and Lundblad, that it may be a delayed symptom, coming after the obstruction

has been diagnosed Lundblad's Case 3, a patient suffering from mitral stenosis and auricular fibrillation, suddenly developed "a feeling of numbness in his right leg. He was immediately put to bed. After a short while he had a similar feeling in his left leg, followed about a quarter of an hour later by intense, gradually increasing aching pains in his right leg, mostly in the calf and foot. There was an aching pain in his left leg as well, though not by far so intense as in the right one." When taken to hospital next day, still suffering from severe pain in the right leg and foot, the right leg was discoloured and paralysed. Pulses were felt in both groins but the right one was weak. At operation, a clot was found extending from directly below the bifurcation of the aorta into the right common femoral artery, this was removed and at the post mortem a fragment was found at the aortic bifurcation. The case illustrates delay in the appearance of pain, and also that pain occurs in the ischæmia territory, which in this case was at first bilateral and later right-sided.

James (11), writing in 1830 before the introduction of anæsthetics, describes a patient in whom he tied the left superficial femoral artery for aneurism of the left external iliac artery. The tumour increasing, he put a ligature around the aorta. It was drawn tight, and the tumour became flaccid, "at the same time the patient complained of deadness in the lower extremities." After the operation "he complained of great pain in both the lower limbs, which on the aneurismal side soon increased to agony, and although opium was repeatedly given, it did not cease till he died." The pain was chiefly at the knee. The ligature was found to have been tied immediately below the inferior mesenteric artery. In this case the actual ligation of the aorta gave rise to no pain, this developed later and especially in the leg to which, owing to aneurism and previous ligation, little or no collateral flow could become established. Murray (12) relates how, without anæsthetic, he tied below the inferior mesenteric artery the aorta of a man whose right limb was insensible and pulseless owing to an aneurism of the right iliac artery. "The tightening of the knot did not seem to occasion any great pain, nor to cause any unusual sensation or shock in the vascular, nervous, or respiratory systems. His first complaint was, that his left leg had become as benumbed and useless as his right." Next day, and before his death, this patient was suffering severe pain in the lower extremities.

Obstruction of arteries of the limbs

Of the many cases of embolism of arteries of the limbs that have come under my own observation I have been impressed by the fact that pain, as an early symptom, is confined to cases in which a large artery is involved, and in which conspicuous signs of ischæmia of the limb develop. Thus those emboli, which in cases of subacute infective endocarditis so often lodge in vessels of the order of the radial, ulnar, or smaller arteries, do not give rise at the time to pain, and frequently pass unnoticed unless the

superficial vessels are searched regularly, or unless signs of superficial inflammation subsequently appear. This definite impression from personal experience is substantiated by past records. It is sufficient to peruse such series of collected cases as those published by Lapinsky (19), Key (18) and Jefferson (17), to find case after case displaying pain in combination with accepted manifestations of ischæmia, with numbness of the limb, motor weakness, or the discoloration and lowered temperature that threaten necrosis, so also when we deal with numerous isolated case records. There are occasionally records in which pain is mentioned and emphasised as an early and severe symptom without reference being made to sensory or motor loss, but none that I have found in which such pain is definitely stated to have been unaccompanied by paralysis. The relation is too complete to be accidental or to be without important significance. The association with paralysis is easy to understand if we acknowledge pain also to arise out of ischæmia. And the reason why pain is a feature of the obstruction of large arteries is not that the periarterial tissues of these are more sensitive than those of smaller vessels, but that the ischæmia of a limb is the more severe, involving also more of the muscle of the limb, the nearer to its origin the main vessel is obstructed.

The case may be one of mitral stenosis with auricular fibrillation in which broken clot is subsequently found in the heart, or it may be one of typhoid fever in the third or fourth week of the disease (Patry (29), Lapinsky (19, Cases 2 and 6)). If we accept these as typifying embolic and thrombotic obstructions, or if we prefer to distinguish the embolic and thrombotic clots from accounts of their naked eye appearance in the individual cases, we shall conclude that their symptoms are indistinguishable, and that it is the obstruction and not the manner in which it is brought about upon which pain depends.

In regard to the location of pain, which is nearly always described as severe, the following illustrations will suffice for the limbs.

Axillary and brachial artery In Neuhof's case (25) of obstruction to the axillary artery, the pain is stated to have been in the hand and arm, and in Wideroes's (33, Case 1), from shoulder to lower arm. In blockage of the brachial artery Jefferson (17, Case 3) reported pain in the hand, Pearse (30, Case 4) in fingers and forearm, Banks (14) just above the elbow, and Key (18, Case 5) in the hand and lower arm.

Common iliac artery While Danzis (15) reported pain in the groin from obstruction of this vessel, Lundblad (22) reported it in the foot and in the leg to the knee in one case, and in the leg and heel in another.

Common femoral artery Wideroes described the pain of obstruction of this artery as in inner thigh and popliteal region (Case 3) and in the upper thigh (Case 5). But in Key's Case 1 and Olvecrona's case (28) it was in the region of the knee, in the cases of Key (Case 4), Aleman (13) and Pearse (30) in the lower leg, and in the two cases of Lapinsky (19, Cases 3 and 4) and in that of Watson (32) in the foot.

Popliteal artery The pain from an obstructed popliteal artery was in the lower leg in Leyden's case (20) and Key's Case 6 and in the lower leg and foot in Lapinsky's Case 6, in Key's Cases 3 and 4, Söderlund's Cases 1 and 2 (31), Odelberg's case (26), and Pearse's Case 2, it was in the foot

Thus the pain is almost always beyond the obstruction and not in its immediate vicinity, it differs in situation in cases of obstruction of the same vessel, it can occur in the foot whether iliac, femoral, or popliteal artery is blocked, facts inexplicable on the basis of the local origin of pain, but readily understood if it arises out of ischæmia. The site of pain has in fact little value in locating the clot

Pain is the symptom chiefly emphasised in reports of obstruction to a main artery of a limb, and it is customarily described as sudden in onset and severe, and accompanied by numbness and loss of power. Thus it is often inferred, or actually stated, that sensory or motor loss comes suddenly and the impression may be gained that these symptoms cannot precede pain. Reasons have already been given for questioning these ideas. It is consistent with the hypothesis of ischæmic pain, that pain should come before sensory loss, and also that the order should be reversed and that sensory loss should precede pain. In Pearse's sixth case an embolus of the common femoral artery led to tingling, numbness and paralysis of the leg, but no pain followed, in Gejrot's case (16) and in Key's second case numbness was the sole complaint. The onset with numbness and subsequently developing pain is more frequent (*see* Case 2) and it is notable that a deliberate statement of this order of development is found most often in the more detailed and careful descriptions. Thus in describing his second case Lundblad (22) says — "She suddenly had a feeling as though her right foot was growing numb. At first she had no difficulty in moving her leg nor did she have any pain. But after a couple of hours an aching pain set in which rapidly became aggravated and reached a violent intensity. It was localised mostly to the foot and leg, but was also felt higher up, slightly above the knee." Seen a little later the leg was pale, marbled, pulseless and largely anæsthetic. Clots were removed at operation from the iliac artery. This report is not exceptional in type, in Jefferson's Case 1 (17) of a clot in the axillary artery, pain in the arm was preceded by tingling and numbness, in Pearse's Case 2 (30), embolism of the vessels of the leg gave numbness of the foot, and pain 15 min later, in Key's Case 1 (18) of obstruction of the common femoral artery, the onset was with numbness, succeeded by pain in the popliteal space, similarly in two of Lundblad's cases (22), in Olivecrona's case (28), and in Söderlund's case (31). A significant history is that given by Wideröes's first patient (33), who was wakened by pain and found numbness.

A perusal of the case records suggests that numbness or weakness is more likely to be noticed as a first symptom by those at rest in bed, that pain is more likely to mark the onset in those who are up and using the limbs, and that pain may follow numbness at rest when the subject moves or is manipulated. Such forms of onset would be in entire harmony with

the origin of the pain in ischæmia, but these details are as yet not clear enough to allow final statements to be made

Among past records are to be found the reports which now follow, reports which seem to me to be conclusive in the evidence they bring for the ischæmic origin of the pain discussed

Jefferson (17) describes how a man of 42, while being moved a day after operation for umbilical hernia, complained of tingling and increasing numbness in his arm, which rapidly developed into intense and persistent pain with complete paralysis of the arm. When examined the arm presented clear signs of an obstruction to the circulation in the axillary artery. This artery was exposed 2½ hr after the onset of symptoms under local anæsthesia, the vessel opened between clamps, and the clot removed. Release of the upper clamp caused a flow of blood, release of the lower clamp caused a flow of blood after the removal of another clot. The artery was stitched up and the two clamps removed. The patient immediately said, "The pain has gone," and a few seconds later remarked that "he could move his fingers, and that his arm was warmer." The radial pulse soon felt full and free. Here is an instance of intense pain in the arm continuing for 2½ hr, the clot was removed, each clamp was released separately, and without relief. Relief came when both clamps were opened and in the instant when the circulation to the limb was restored. This exceedingly interesting record does not stand alone. It is fully substantiated by similar reports of relief of severe pain by embolectomy under local anæsthesia published by Olivecrona (28), Odelberg (26), Aleman (13) and Lundblad (23).

A case described by Key (18, Case 3) is valuable in this same connection. The patient, who suffered from cardiac failure, developed sudden severe pain in the foot with full signs of obstructed circulation in the limb. The embolus was found in the common femoral artery, and in its branches, and was removed with restoration of pulsation. But, although the main clot was gone and the clamps removed, pain persisted. Further exploration now discovered another clot obstructing the popliteal artery. When this was removed and the vessel released the foot became warm, and the pain which had been quite unaffected by removal of the first clot now disappeared completely. Thus, it is the restoration of the circulation and not the removal of impacted clot which relieves the pain. Key describes a second case (Case 5) which illustrates the same point.

It is here to be noted however that the removal of a clot from a proximal part of the main artery may give relief, although the vessel or its branch remains blocked lower down (Key's Case 6), this is to be anticipated on the ground that disturbance to the circulation in a limb is the greater the more proximally the obstruction occurs in the main vessel. The same point is illustrated in the following record. This is Landstrom's first case (21), published in Key's series. A man of 75 years had undergone a prostatectomy a few days earlier. He complained of the onset of severe pain in his right arm, loss of feeling, pallor, and paralysis. Examined half an hour later,

signs of an obstructive clot in the lower part of the axillary artery were found. While this vessel was being manipulated to identify the precise level of the clot the patient abruptly lost his symptoms. Simultaneously the colour of the arm became normal and movement returned to it. Pulsation could now be felt in the brachial artery to the elbow, but the radial and ulnar pulses could not be felt. This is a clear description of dislodgment of a clot from the axillary artery, the embolus now becoming impacted lower down, and probably at the bifurcation of the brachial artery. Relief of pain came at once with the improved circulation to the limb, it is noteworthy too that the embolism of the lower artery, which in this instance could be timed accurately, was accompanied by no pain. In several other instances Lindstrom, and in another instance Ohrstrom (27), obtained similar relief of pain by deliberately massaging a clot onwards in the main artery of the limb.

Effects of local anaesthesia To records of the relief of symptoms of arterial plugging by surgical removal of the clot, records which in recent years have become numerous and have supplied unusually clear details of symptomatology, we are indebted for quite clear evidence that the early pain of arterial obstruction is not caused by stimulation of nerves or nerve endings in the wall of the artery, thus giving rise either to local pain or to pain that might possibly be regarded as referred to a more distal part of the limb, but that the stimulus causing pain has its seat in distal tissues. For it is customary in the case of the limbs to perform this operation of embolectomy after infiltrating the tissues surrounding the vessel with local anaesthetic, so that the vessel is exposed, opened, and sewn up again painlessly. It is abundantly evident from many reports that thorough infiltration of the artery with anaesthetic has no influence on the pain, which persists, as illustrated by several cases already quoted, until, and only until, the circulation through the affected vessel becomes restored.

The tissues in which the pain originates The evidence already given seems sufficiently to establish the conclusion that pain, as an early symptom of embolism, is due to ischaemia. But this conclusion would almost inevitably lead on to the second that the tissue in which pain arises is the musculature of the limb. As indicated in the preliminary remarks of this paper, when the bloodflow to a limb is arrested deliberately for a half hour more or less any pain that follows comes from the musculature. The pain is definitely related to muscular work, it is a continuous ache, often becoming very severe, and is associated with tenderness of the corresponding group or groups of muscles. When pain arises in a working limb, to which the bloodflow has been arrested by embolus, its origin from muscle can scarcely be doubted (Case 1). In most case reports where pain is recorded its site is not precisely stated, and other characteristics are rarely mentioned. But such information as is available is not only consistent with but supports the view that the pain at least usually is muscular. There are clear indications in many case records that the pain increases quickly to become

intense, and that it then becomes a continuous pain with little variation in degree. Such are the characteristics of pain starting from ischæmic muscle. Another characteristic of the pain of muscular ischæmia, when this is produced experimentally, is its almost instant subsidence on release of the circulation, which as has been seen also happens when arteries are freed from clots by the operation called embolectomy. Another very suggestive fact is that tenderness is easily elicited by pressure over the muscles involved. This was noticed by Lapinsky (19) in several cases, by Leyden (20) in his case, and by myself in several patients (*see* Cases 1 and 2). References to the complaint of cramp, or of cramp-like pain, by Ohrström (27), Bocherini (10) and Hawkins (5), and in several cases recorded or cited by Martin-Durr (24), and the diffuseness of the pain that is obvious from other descriptions, definitely favour the view of its muscular origin.

We may supplement the previous conclusion by saying that it is the ischæmia of somatic muscle that is usually, perhaps always, responsible for the pain under discussion.

GENERAL CONSIDERATION OF THE INITIAL PAIN OF EMBOLISM

Limbs In the main part of this paper, we have arrived at the conclusion that the initial pain of embolism (and of thrombosis) of limb arteries is due to ischæmia, and that the ischæmic tissue responsible is usually, perhaps always, voluntary muscle.

To link up this conclusion with corresponding conclusions relating to other organs, we may pass briefly in review from the same standpoint the effects of plugging of arteries supplying the chief viscera.

Brain It is recognised that embolism and thrombosis of the main intracranial arteries usually happens quite painlessly.

Heart The best known symptom of thrombosis or embolism of the coronary arteries is anginal pain, pain rising quickly to what is usually a severe level, pain which is characteristically continuous and long lasting. Evidence concerning this pain has been considered in recent years with unusual care and in detail, the reasons for concluding that it originates in ischæmia of cardiac muscle, have been discussed in a recent paper (*see* 50).

Lungs Pain is not a recognised symptom either of embolism or thrombosis of branches of the pulmonary arterial system.

Spleen It is legitimate to conclude from the rarity with which splenic infarction is diagnosed during life that embolism of its vessels causes no characteristic initial pain, when pain occurs in the left hypochondrium it is probably rightly ascribed to local inflammation of the peritoneum following as a sequence to embolism.

Kidney Although embolism of a renal artery is usually followed by little or no pain, pain, and even severe pain, in the back or loin is sometimes recorded.

Mesenteric arteries The recognised symptoms of obstruction of the superior mesenteric vessel are abdominal pain, vomiting, constipation or

bloody stools, distension, and collapse. Very many reports are available, numbers were collected by Faber (35) in 1875 and since by Watson (47), by Jackson, Porter and Quinby (40) and by Welch (48). Using such reports as include post-mortem records it is clear that abdominal pain is an early and usual symptom. It may not occur, but occurring it is almost always described as severe, and is sometimes spoken of as colicky in type. Another feature is that it increases in intensity and is long drawn, continuing for hours or even days. It seems to be diffuse and difficult to locate, is most usually referred to the region of the navel, though not infrequently to other parts of the abdominal wall such as epigastrium or hypochondrium.

Agreeing with pathological evidence, experiment on animals has shown that so far as adequate blood supply is concerned the mesenteric branches are almost end-arteries and that ligation of one of these is constantly followed by contraction of the corresponding section of bowel (Litten (42), Mall (44)). The fact is easy to verify, and I observe that the contraction is not rhythmic but tonic. Jackson and his collaborators say that the pain is generally admitted to be due to intestinal contraction. Welch, who had closely studied available records, also held this view of the pain in its initial phases. Strong contraction of the bowel is well known to result in pain. Ischæmia provokes contraction which is long continued, by preventing the removal of a chemical pain factor, such as is supposed to underlie ischæmic pain, it should ensure continuity of the pain and cause it to become gradually enhanced, as has been recorded of these cases. Variation in the site of pain may be attributable to the great length of gut from stomach to colon, which the superior mesenteric artery supplies. The view that pain is induced by disturbance in the walls of the gut, rather than in the walls of the artery is supported by the observation, sufficiently established (Fagge (36), M'Weeney (43), and other cases to be found in Jackson's collection) that thrombosis of the mesenteric or of the portal vein gives pain indistinguishable from that of arterial embolism.

As long ago as 1834 Kussmaul (41) suggested that the site of pain might possibly serve to differentiate between obstruction of the superior and the inferior mesenteric vessels. Pain would be expected, and as we have seen is often found, to be referred to the region of the navel in the former, while tenesmus and pain from the bladder might be expected in the latter. But the symptomatology in the latter is not known sufficiently even to-day to allow of its clear statement or differentiation, though it is clear that severe pain is amongst the symptoms (39).

Comment

To sum up, pain as an initial and severe symptom of embolism (or of thrombosis) is the rule when the artery supplies a limb, the heart, or the bowel. Embolism (or thrombosis) of an artery supplying brain, lung and spleen, occurs painlessly. The organs first named all contain a large proportion of muscular tissue, the organs last named contain none or little

The renal arteries, embolism of which seems sometimes to give rise to severe pain, supply renal tissue, but they also supply the muscular pelvis of the kidney, we have no information allowing us to conclude that the presence of this muscular tissue explains or fails to explain the renal symptoms. The broad grouping of organs into those which are muscular and give rise to pain, and into those which are non-muscular and give no pain, and the highly suggestive evidence, especially in the case of limb and heart, that the pain discussed arises from ischæmia of muscular tissue, warrants a final general conclusion, namely, that the early pain of sudden arterial obstruction is generally, if not always, due to muscular ischæmia.

CONCLUSIONS

In embolism of an artery of a limb, pain and tenderness may occur in the region of the clot as a late symptom, this is especially frequent when the clot is infected, and is attributable to inflammation. But the early and often severe pain of embolism here considered arises differently.

This early pain is not due to impact, nor to any other physical change stimulating nerves or nerve endings locally, as has been supposed. It is usually felt in the limb distal to the obstruction. An interval elapses, usually if not always, between the onset of circulatory arrest and the onset of pain, which is not necessarily the first symptom. The interval, though very variable in duration, is usually measured in minutes. The pain occurs after an obstruction in an artery of sufficient size to induce conspicuous signs of ischæmia of the limb. The pain is the result of ischæmia, and it is ischæmia of muscle in the limb that is usually, perhaps always, responsible.

Embolism (or arterial thrombosis) gives rise to pain when it affects muscular organs, like the limb, the heart, or the bowel, but not when its effects are confined to non-muscular organs like the brain, the lung, or the spleen. Thus the early pain of sudden arterial obstruction is generally, if not always, due to muscular ischæmia.

CASE REPORTS

Case 1 Sudden obstruction of left femoral artery, first symptoms, including pain in heel and numbness, noticed while walking a short distance. The pain was for the most part distal to the obstruction.

T S, a man of 61 years was admitted as an inpatient on January the 17th, 1935, presenting the signs of aneurysm of the ascending aorta of syphilitic origin, venous congestion, auricular fibrillation, enlargement of the heart, high blood pressure (210 systolic, 105 diastolic), but no valvular disease. He was given digitalis and rest and his congestion soon responded well to this treatment. He became convalescent.

February the 9th. At 9 a.m. the patient walked 40 yards to the ward lavatory, stood and washed himself for 10 min. and had walked back almost the whole way to his bed, when he noticed a pain starting suddenly in the inner side of his left heel, this grew in severity and gradually spread up the leg to the inner part of the thigh. It was a dull aching pain, it was not very severe. Closely questioned he said that while walking back to bed he noticed numbness of his foot. As soon as he reached his bed he called the sister of the ward to examine his foot, she found it anæsthetic. The pain in the thigh lasted about 3½ hr., that in the leg lasted much longer. 10.30 a.m. On examination no numbness could be detected, the patient stated it had cleared away. The left foot and leg were colder, a little paler, and more cyanotic than the right. Pulsation was just palpable in the left femoral artery, but in none of the other arteries of this leg.

February the 10th Numbness had returned to the foot, which remained cold and pulseless

February the 11th The left foot and leg were of a little deeper and more cyanotic colour than the right. The left foot was much the colder, and a difference in temperature was traceable as high as the knee. The pulsations of both arteries of the foot, of the popliteal, and of the femoral artery, were easily felt on the right side, on the left only a feeble femoral pulse was felt above Poupart's ligament, it could not be traced below the ligament as it could on the 9th. The common femoral artery could be felt as a solid cord in Scarpa's triangle. The left foot was considerably but not absolutely anæsthetic, sensation gradually improving to normal at the junction of the upper and middle third of the leg. Needle pricks were felt very imperfectly on the foot, but normally after the middle of the leg was passed. The sole of the foot was a little tender. The belly of the gastrocnemius muscle was tender when squeezed, the muscles on the front of the lower part of the leg were exceedingly sensitive to pressure. All these muscles were flaccid.

February the 12th The anæsthesia had declined a little in extent. Otherwise the signs were unchanged. The patient was unwilling to dorsiflex the ankle owing to pain produced on the front of the leg, plantar flexion was undertaken but was also limited by pain. There was still some pain across the root of the toes.

Course By the 4th day all pain had gone, tenderness of the muscles on the front of the leg persisted till the 34th day. The anæsthesia began to decline on the 12th day and continued to do so steadily until the 52nd day when only a little remained on the dorsal surfaces of the first two toes. Simultaneously and gradually his motor weakness disappeared, it was most conspicuously shown in dorsiflexion of the ankle, this was still detectable, though he walked without limping, on the 52nd day, when he left hospital.

Comment This case was one either of thrombosis or of embolism of the left common femoral artery. It was clearly established that numbness came at least as early as pain, from which it is to be deduced that the arterial occlusion preceded the onset of pain by very many minutes and probably at about the time when the man left his bed on his way to the lavatory. The slight and temporary recovery of sensation suggests that an embolus may have moved on from the common into the superficial femoral vessel. The subsequent reappearance of numbness in the leg is explained by extension of thrombosis back into the common femoral vessel at least as far as Poupart's ligament. The signs in the groin were those of a local clot, but this man's pain began in his foot and continued chiefly in foot and leg, he also suffered from long continued tenderness of muscles of the leg. The pain could not be connected directly with the vessel wall surrounding the thrombus. The pain began and was felt as a continuous pain while the man walked, it continued although the man rested, these facts the character of the pain and its association with tenderness, suggest its origin in ischaemia of muscles.

Case 2 *Permanent femoral obstruction, in which the first symptom was paralysis of the leg, pain developed in the lower leg 12 hours later, after warming the leg, the pain was distal to the obstruction*

D T, a married woman of 29 years, suffering from mitral stenosis and fibrillation of the auricles, was admitted to hospital and delivered of her first child, on *December the 12th, 1934*

December the 16th At 12 30 *a m* she awakened for an unknown reason, and shortly afterwards noticed that her right leg felt numb. There was no pain 6 45 *a m*. She still complained of paralysis and numbness of the right leg. On examination the leg was found to be pale and cold as high as the knee. She could bend her knee weakly, but not her ankle or toes. Sensation to touch and prick was impaired over the foot, her leg was very tender to pressure. The right femoral pulse was a little weaker than the left. The popliteal pulse and the pulses of the foot were palpable on the left but not on the right side. 12 *noon*. An electric cradle was fitted over the right leg and shortly afterwards she began to have an aching pain in the front of the lower leg, this lasted about an hour.

December the 18th and 20th Anæsthesia was still present over the whole foot and analgesia over the distal half of the foot. Plantar flexion of the ankle and toes was present dorsiflexion was nearly absent. Movements at the knee were powerful. The pulses were unchanged. The oscillogram gave good excursions above and below the left but none above or below the right knee. The femoral arteries were equally palpable to a point two inches below Poupart's ligament.

January the 2nd The area of impaired sensation was smaller.

March the 21st A little numbness remained between toes 1 and 2 and on the heel of the right side. Voluntary movements at the ankle were still limited and the leg muscles were wasted. The pulses were as previously noted.

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OBSERVATIONS ON URTICARIA PROVOKED BY EMOTION,
BY EXERCISE AND BY WARMING THE BODY *

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In the following paper we describe observations on a group of cases illustrating a well defined type of urticaria which hitherto has not been generally recognised though, from time to time, isolated instances have been reported. Briefly, its main features are that the urticarial attacks are regularly induced by emotion, exercise or by warmth, they are characterised by the development of numerous small flares and minute wheals and usually accompanied by itching. Its chief interest, however, is that our observations have shown clearly, we think, that the H-substance responsible for the urticaria is released in the skin through the peripheral nerves.

These observations arose out of a case (Case 1) which was brought to our notice by our colleague, Dr H W Barber, and which seemed to belong to the category of the so-called psychogenic urticarias, the eruption being easily provoked by emotional stimuli. We found, however, that while emotional stimuli were quickly followed by the appearance of scattered wheals and flares on the skin, much more profuse eruptions were readily provoked by exercise and by warming the body. The regularity with which these attacks could be induced under controlled conditions allowed us to proceed with the analysis of the factors involved in the production of the urticaria, this analysis provided clear evidence of the participation of the nervous system.

Through the kindness of our colleagues† we have since been enabled to investigate five other cases of the same type, and these observations have confirmed and extended those made on the first case. The histories and clinical features of all these cases are so alike and our observations have yielded results so concordant, that we need not describe each in detail. The case histories are summarised below, we then give a general description of the group and illustrate our observations by example.

* Work undertaken on behalf of the Medical Research Council

† We are indebted to Dr A F Hurst for Case 2, Mr E B French for Case 3, Dr G B Dowling for Case 4, and to Dr H W Barber for Case 5

Case histories

Case 1 E.A., a healthy looking, well developed, single woman, aged 22, was admitted to Guy's Hospital on February the 28th, 1935. She complained of attacks during the last 6 years of a blotchy rash on the skin in which small lumps develop and which are accompanied by a feeling of warmth and intense itching. The rash comes quickly whenever she is excited, flurried, embarrassed, or when she gets a start. It comes also whenever she goes to a dance the eruption developing when she dances and subsiding when she sits out, even the excitement of preparing to go to the dance is sufficient to bring on an attack. If she is late for work in the morning and runs to catch a bus, an attack often comes. The frequent blotching of her face and neck causes her considerable distress as she thinks people avoid her as suffering from some contagious disease. She is easily embarrassed and blushes and sweats readily. The attacks bear no relation to menstruation, to the season of the year or to food though occasionally one comes when she sits in front of the fire after her evening meal. An attack sometimes comes after a hot bath or a long walk. She has found that the attacks are less frequent and milder if she leads a quiet life, avoiding excitement and hurry.

In slight attacks only a few blotches and lumps appear, these subside in a few minutes. In bad attacks, the whole skin of the body, except that of the palms and soles, becomes flushed itchy and lumpy, it may be an hour or more before the skin returns to normal. Even in bad attacks she has never felt ill or giddy or suffered from headaches. Apart from these attacks, and measles and chicken pox in childhood, she has always been well. The patient cannot attribute the beginning of the rash to any particular event in her life. She smokes about 5 cigarettes a day but does not drink alcohol since she has found that it always brings out the rash. There is no history of skin trouble, asthma, or hay fever in her family, her mother, father and one brother being alive and well.

Examination revealed no abnormality of the chest or abdomen, the nervous or genito urinary systems. The systolic blood pressure was 125 and the diastolic 85 mm Hg.

Case 2 E.G., a typist, aged 20, unmarried, attended Guy's Hospital as an outpatient on April the 10th, 1935. She complained of severe itching and a blotchy rash in the skin with small lumps the size of lentils which are white and raised. The rash is quickly brought out if she is excited or frightened, or if she laughs a lot. Whenever she goes to a dance she has to stop half way through because of the rash appearing, it soon goes when she rests. Attacks always come if she runs upstairs, or for a bus, or even walks smartly, and sometimes after a hot bath. Sometimes she has queer feelings in her head and then her face seems stiff, she becomes frightened and the rash quickly follows. She also gets a slight attack on the face and neck if she tastes anything acid such as an orange or vinegar, even the smell of vinegar is sufficient. She often has an attack when in bed, it always accompanies a dream that she is running or frightened, she awakens itching and finds the rash on the skin. The attacks are worse in summer than in winter, they are less severe when she is menstruating. The rash seems to start in the neighbourhood of the larger joints and spreads over the body, except the palms and soles. In bad attacks she is covered with "pimples" from head to foot, sometimes she feels sick and giddy and may faint, afterwards suffering from headaches. A bad attack may end in shivering. She blushes but does not sweat easily.

During the last two years the attacks have been more frequent and more easily brought on, and, though she leads a quiet life cannot entirely avoid them. Except for chicken pox at the age of 3 and these attacks, which began at the age of 12, she has always been well. There is no personal history of other skin trouble, asthma, or hay fever, a third cousin has asthma.

Examination shows her to be a spare but well developed and healthy girl. There is a slight enlargement of the thyroid isthmus, signs of thyrotoxicosis are wanting.

Case 3 M.F., a single woman, aged 18, first attended this Hospital on October the 24th, 1935. Since the summer of 1934, she has suffered from attacks of an itchy red rash with small white lumps on the skin. This rash appears mostly on the arms and thighs, above the knees, and sometimes on the face, she has not noticed it on the trunk. The white lumps only come in bad attacks. The rash comes when she takes exercise, specially tennis, and when she is hot or agitated. She has occasionally had it when dancing, but not badly. When she lies a long time in a hot bath, she gets itchy red patches all over the body. If a bad attack is provoked on one day by playing tennis, then the next day she will have little or no rash even with the same amount of tennis. The rash is always worse if she has not recently taken exercise. She knows of no reason for the onset of this trouble. About five years ago she had occasional swelling of the face with large white "bumps" when she went out into the cold. This was attributed to eating eggs and when she stopped eating them, this swelling did not recur. There is no personal or family history of asthma, hay fever, or skin trouble.

She is a well developed, healthy and intelligent girl and not emotional or nervous.

Case 4 D B, a single young woman aged 20, first attended this Hospital on November the 22nd, 1935. About 3 years ago she bathed when she was very hot, the skin became reddened and many white lumps, about the size of a match head, developed. There was very little itching but she felt as if her skin was tight. This rash disappeared in about half an hour. Before this time she had always been perfectly well, but since then the rash has returned whenever she takes exercise, it comes also with dancing with a fright, or a blush. She can usually ride horseback without getting the rash. Exposure to the wind will bring the rash on the face. She always gets a bad attack after bathing in the sea. The rash comes all over the body except on the palms and soles. It sometimes makes her feel giddy, and she often feels shivery as it is passing off. She dislikes the attacks and has recently led a restricted life to avoid them. She finds now that the rash comes with very little exertion and sometimes without any obvious cause. On one occasion last summer, after eating an ice cream her lips swelled up. She has since avoided ice cream.

She is a well developed and otherwise healthy girl, of a rather nervous temperament. She has never suffered from hay fever or asthma, two maternal aunts suffer from hay fever and two uncles and an aunt have asthma, a first cousin had eczema.

Case 5 M V, a married woman, aged 33 attended the Out patient Department of this Hospital on November the 27th 1935. For the last four months she has been troubled by a red and very itchy rash on which many small white pimples appear. This rash comes daily when she gets hot and usually only in the evening when she works as an office cleaner. It comes also if she runs upstairs or to catch a bus and sometimes when she gets annoyed. She has not noticed it to come during or after a hot bath. The rash appears first on the face and then on the arms, in bad attacks it spreads all over the body except the hands and feet. It lasts about half an hour and as it goes away it leaves a bad headache which lasts for some time. She cannot think of anything which might have brought on the trouble. It has become worse recently, and causes her considerable embarrassment. Before the onset of the rash she had always been perfectly well and, apart from it, still is so. Her husband and two children are well, her father suffers from asthma.

Physical examination reveals no abnormality. The patient is a healthy, well developed woman and not emotional or nervous.

Case 6 G H a public school boy, aged 18, attended this Hospital on December the 1st, 1935. For two years he has been troubled by a slightly itchy rash which comes on the chest and back whenever he gets hot either by taking strenuous exercise, such as squash or football, or by soaking in a really hot bath. The rash comes in red patches about 2 cm across and on these small white lumps develop about 2 mm in diameter. The whole rash disappears in about half an hour. The rash comes only on the trunk above the waist. He has never seen it on the arms or legs. Excitement occasionally brings a few red blotches. If he plays squash hard one day and has a rash, an equally hard game the next day produces none.

Two years ago when sunbathing he exposed himself too long, the skin peeled from his shoulders and chest, but not from the back or arms. A month later the rash began on the chest and six months later involved the back also. Apart from the rash he is and always has been perfectly well. His father sometimes has urticaria and his mother suffers from hay fever.

Description of attacks

These patients complain of repeated and transient attacks of a red and itchy rash. We have witnessed many of these attacks and their characters are remarkably constant. The elements of the eruption consist of small flares 1 to 2 cm in diameter, in the centre of which wheals form 1 to 2 mm across. When the stimulus provoking the eruption is a short one, for example a needle prick, the interval between the cessation of the stimulus and the first appearance of the flares is about 2 minutes, the wheals forming about 1 minute later. The flares and wheals subside within an hour. The urticarial response thus closely resembles, in appearance and in time relations, that following the pricking of a dilute solution of histamine into the skin, and, from the work of Lewis and his colleagues (8) is interpreted as due to the release of H-substance in the skin. Often several flares coalesce, and on the irregularly shaped flushes so formed several separate wheals develop.

When very numerous, the wheals also coalesce and are then irregular in outline. Sometimes, as in very slight attacks, wheals do not develop on the flares which, fading rapidly, leave behind small red spots 1 to 2 mm in diameter. Also, on the lower parts of the extremities, the flares tend to be indistinct, even in severe attacks, and here red spots may alone become manifest. Apart from slight puffiness of the eyes and lips, there is no swelling of the subcutaneous tissues as in angioneurotic oedema.

Although there are local factors, to be referred to later, which modify the distribution and intensity of the eruption, the rash appears and spreads symmetrically on the two sides of the body. It usually comes first on the blush area and spreads down the trunk and limbs, developing on the arms before the legs. The wheals tend to be more numerous about the flexures, as on the anterior axillary folds, in front of the elbows and wrists and behind the knees. This, however, is inconstant, for, regions showing many wheals in one attack show few if another attack happens within the next day or two. So that the profuseness of whealing in any area varies from time to time.

It is convenient to describe the attacks as slight, moderate, and severe. In slight attacks scattered flares and wheals appear mainly in the blush area. In moderate attacks they are more numerous and widespread, but the forearms, legs, hands and feet are usually spared, though here, specially about the joints, a few flares and wheals or red spots alone may form. Even during severe attacks, in which almost the whole skin is whealed, the hands and feet are not involved to the same extent as the rest of the body. Scattered wheals are present on the backs of the hands and feet, fingers and toes, but the palms and soles are always unaffected, and our patients have never experienced either swelling or itching here. The hairy parts of the axillæ are also entirely, or almost entirely free, when epilated they are occasionally slightly flushed, and may show a few red spots and wheals. Usually, the epilated axillæ are strikingly pale and free from rash in contrast to the surrounding deeply flushed and much whealed skin. We may note that Cases 1 and 2, whom we questioned, denied using any preparation in the axillæ. The scalp becomes flushed, though not so deeply as the body skin, and wheals are recognisable where the skin is loose, as at the nape of the neck. The hairy pubic area is also flushed though wheals are sparse.

Usually, the outbreak of the eruption is accompanied by itching, and this may be very intense. On occasion, even in a severe attack, itching is not experienced. When the eruption is very profuse, the complaint is sometimes not of itching but of a burning feeling in the skin.

All six cases are of the same type, but not of equal severity. Severe attacks with whealing of almost the whole skin have been witnessed in Cases 1, 2, 4 and 5. In Case 3, the attacks are never more than moderate, the wheals though widespread over the body being less numerous than in the other cases. The attacks in Case 6 are always slight, there being at the most about 80 wheals distributed over the chest, back, neck and face. We confirmed his statement that flares and wheals did not come on the arms.

and legs or below the waist Case 4 differs from the others in that she suffers in addition from an urticaria due to cold This is discussed later (See page 269)

Three of the patients complained of general symptoms accompanying severe attacks, giddiness (Cases 2 and 4), sickness and fainting (Case 2), shivering (Cases 2 and 4), and headache (Cases 2 and 5) On several occasions during severe attacks induced by warming the body, both Cases 1 and 2 became pale, giddy and faint, the heart rate being slowed, both recovered quickly on lying down We saw shivering during the severe attacks provoked by exercise and by warming the body in Case 2 and in those provoked by the subcutaneous injection of doryl in Cases 2, 4, 5 and 6

We shall now consider the factors provoking the urticaria A point of importance to be borne in mind in this respect is that the too frequent repetition of the attacks leads to a temporary diminution in their severity This is specially so in the case of severe attacks We shall deal with this in greater detail later (See page 266)

Factors provoking the eruption

The patients themselves are quite certain that the attacks are induced by emotion, exercise or warmth, or by a combination of these, and their statements have been confirmed in each case

Emotional stimuli As examples of attacks following emotion, we give the following When Case 1 was embarrassed by exposing her body to a class of students, she blushed deeply In the blush, several deeper red blotches quickly appeared and, as the blush faded, these stood out as bright red flares against the surrounding paler skin In the flares, wheals 1 to 2 mm in diameter, soon developed A few flares and wheals appeared on the abdomen Again, when Case 2 was similarly embarrassed, she blushed slightly, 10 flares and wheals developed within 7 minutes, 2 on the neck, 2 on the right side of the chin, 3 on the right, and 1 on the left shoulder, 1 on the left forearm and 1 on the inner side of the left breast In both patients, this stimulus provoked the urticaria on each of several repetitions We have seen similar slight attacks in all our patients, in response to emotional stimuli

Because of the ease with which emotional stimuli led to the appearance of the rash, it was found necessary for the further analysis of the condition, to accustom the patients to their surroundings and the procedures adopted Thus at first, in the severe cases, such stimuli as the compression of the arm by suddenly inflating a sphygmomanometer cuff, the introduction of a hypodermic needle into the skin or the statement that an injection was about to be given, quickly caused a few flares and wheals to appear Our patients co-operated readily with us and soon submitted to even uncomfortable procedures without more appearing than a transient blush and, at times, a few scattered wheals and flares Usually, when they came to the laboratory, a few wheals were already present or appeared within a few minutes It has been our custom to allow these to subside before proceeding

Exercise In all our patients, exercise, such as running, skipping and hopping, regularly provokes an urticarial eruption more profuse than that following an emotional stimulus. For example, Case 2 skipped vigorously for four minutes. The skin was then flushed generally and moist with sweat, many wheals were appearing. Three and a half minutes later, the skin was covered with wheals. They were sparse on the lower forearms, legs and the backs of the hands and feet, the palms and soles were unaffected. The axillæ were also spared and were pale in comparison to the surrounding skin. The eruption was much faded 13 minutes later.

Warming the body On one occasion we noted, while soaking the arm of Case 1 in hot water to try to produce a local urticaria, that although no wheals developed on the warmed arm, yet many appeared elsewhere on the body. We have found that in all our cases soaking the limbs in water at about 45°C, until the body becomes warm, regularly induces an attack of urticaria, except on the immersed parts. In the more severe cases, the eruption begins after 10 to 15 minutes warming, in Cases 3 and 6 longer is required. In general, the longer the warming the more profuse the eruption, although the wheals first developing subside as later ones appear. The eruption of fresh wheals can be checked by taking the limbs out of hot water and cooling the patient in a draught of air or by replacing the hot water by cold. If the circulation to the warmed limbs is arrested while they are warmed, no urticaria follows, either on the body or on the limbs after restoring the circulation.

The following is an example of a severe attack induced by warming for an hour. In Case 1, the legs were heated in water at 45°C, the body was covered with waterproof sheets to prevent loss of heat through evaporation of sweat. After 10 minutes, the skin was flushed and general sweating had begun. At 15 minutes, wheals began to form on the face, neck and trunk. At the end of an hour the face was blotchy and slightly swollen about the eyelids and lips, and the patient complained that her face felt stiff. The skin of the body, arms and legs (down to the water line) was covered by very numerous and closely set or confluent wheals. There were many minute and discrete wheals, and red spots without wheals, on the backs of the hands and a few on the backs of the fingers. The palms were unaffected, the axillæ, except for a few scattered red spots were free from rash, and were strikingly pale in contrast to the surrounding skin. There was no whealing on the legs below the water line. Half an hour later, the eruption was subsiding. The patient said that she had never before experienced so severe an attack.

General remarks

In this group of 6 patients, whose histories are all very similar, a characteristic type of urticaria is regularly provoked by emotion, exercise and by warmth. Five of the patients are between the ages of 18 and 22 years, while one is 33 years, five are females. The duration of their com-

plaint ranges from 4 months to 8 years. Only one, Case 6, can suggest an origin for the urticaria, in his case it followed a month after sunburn. It is of interest to note that in four cases, there is a family history of asthma, hay fever, urticaria or eczema.

A number of previously recorded cases are apparently of the same type, for example, those of Prins (15) (female, aged 15), von de Roemer (16) (male, aged 21), Vallery-Radot and others (17) (female, aged 30, male, aged 25), Drake (3) (female, aged 30), Duke (4) ("urticaria calorica," male, aged 22), Harris (5) (Case 14, male, aged 24) and Marchionini and Ottenstein (13) (female, aged 18). Several of these authors have provoked the attacks by exercise and warmth. Duke (4) notes that in his case the application of hot water, the nitrogen lamp or diathermy to the skin, caused a general urticaria, he remarks that the urticaria is evidently reflex in origin since the nitrogen lamp provoked a general reaction although the circulation to the arm exposed to the lamp was occluded. Duke (4) also noted that an attack could be cut short by cold air or water or ice. Marchionini and Ottenstein (13) failed to produce a local urticaria with a lamp, but readily induced general urticaria by a sweat bath, or by giving pilocarpine intramuscularly. The repetition of the sweat baths seemed to lead to a lessening of the attacks. Harris (5) provoked the urticaria by a hot air bath combined with pilocarpine. As a result of their observations, Marchionini and Ottenstein (13) attribute the urticaria mainly to a sensitivity of their patients' skin to sweat.

The urticaria arises through the peripheral nerves

In the observations now to be described, we have provoked urticaria by immersing the legs in hot water. If the circulation to one arm is arrested and the legs are heated for about half an hour, a general urticaria develops except on the ischæmic arm. If warming is stopped, the patient cooled, and the circulation restored when the rash is subsiding, then a very intense urticaria quickly develops on the previously ischæmic arm. For example, in Case 1, the circulation to the right arm was arrested by a cuff at a pressure of 160 mm Hg and the legs immersed in water at 45°C. After 12 minutes' warming, the skin was flushed and sweating, flares and wheals were beginning to develop. After 26 minutes' warming, a profuse eruption was present on the body and left upper arm, it was sparse on the left forearm. The feet were removed from the water and the patient cooled in a draught of air. At 30 minutes, sweating had ceased, at 34 minutes the patient said she felt cool, and the urticaria was subsiding. The ischæmic arm was cool, cyanosed and showed many Bier's spots. At 35 minutes the circulation was restored to this arm. A bright reactive hyperæmia quickly spread over the limb and within 3 minutes many wheals were developing all over the deeply flushed skin (except on the palm of the hand and fingers) right up to the line marking the upper margin of the occluding cuff, the patient complained of an intense burning feeling in the arm. Over the area where the cuff had been, the wheals were more numerous than elsewhere and, as they developed, became

confluent so that here the arm was encircled by a broad band of whealing. Below the lower margin of the cuff the wheals were less numerous and remained more discrete but the eruption here was also much more profuse than it had been on the other arm. The palm of the hand and fingers remained unaffected. At no time during the observation was there obvious sweating of the right arm. No fresh urticaria appeared on the body after the release of the arrested circulation. This observation has been repeated several times on Cases 1, 2 and 3 and each time with essentially the same result. Control observations have shown that arrest of the circulation alone, without warming the legs, does not provoke the urticaria.

That the local eruption appears so quickly on restoring the circulation at a time when the general eruption is subsiding, and that it is more intense than it was on the other arm, seems to show clearly that H-substance is released in the skin of the arm while its circulation is arrested, and in response to warming the legs. Further evidence of the release of H-substance during occlusion is obtained by first congesting the arm before arresting its circulation and repeating the experiment just described. When the urticaria begins to develop on the free arm, then, but not until then, numerous bluish spots of local vasodilatation appear in the skin of the congested and occluded arm. These spots increase in number and diameter during occlusion and, when the circulation is restored, they are found to mark the places where the wheals will quickly appear. For example, in Case 2 the left arm was congested at 30 mm Hg for 3 minutes and the circulation arrested by raising the pressure to 160 mm Hg. The skin of the arm was well congested, colour returning quickly to an area blanched by pressure. The body was covered with blankets and the legs immersed in water at 45°C (zero time). After 11 minutes, the patient was warm and flushed and wheals were developing on the body. At 16 minutes, wheals began to form on the right forearm and minute bluish spots appeared in the congested skin of the left forearm. At 19 minutes, these spots were numerous and those first appearing had increased in size. Warming was stopped and the patient cooled by immersing the legs in cold water and opening the room windows. At 24 minutes, the patient felt cool and her skin was dry. The numerous blue spots were clearly visible in the congested skin, some were marked in ink. At 25 minutes, the circulation was restored and a bright reactive hyperæmia at once spread over the arm. Between 26 and 27 minutes, many wheals formed on the left arm, and each spot marked in ink became the site of a wheal. Whealing on the arm was at its height at 30 minutes, as usual it was much more profuse than it had been on the free arm, specially on the site of the occluding cuff. Similar observations were made on Cases 1 and 3.

It follows that the H-substance must be released in the skin through the peripheral nerves, for the nerves constitute the only functional connection between the ischæmic skin where H-substance is released and the body where the stimulus is applied. Proof of this is supplied by observations on Cases 1, 2 and 3, by which it was shown that blocking of a cutaneous nerve prevents

in its area of distribution the development of the urticaria in response to warming the legs. For example, in Case 2 the position of the internal cutaneous nerve above the right elbow was defined by local faradism. The circulation to the arm was arrested at a pressure of 160 mm Hg (zero time) and 5 c c of 5 per cent procaine were injected around the nerve, the injection being completed by 2 minutes. At 6½ minutes, full anaesthesia was established and extended from around the site of injection above the elbow down the ulnar side of the forearm. On the flexor aspect, the margin of the completely anaesthetic area was remarkably sharp and roughly bisected this surface. Its margin on the extensor aspect was bordered by patches of partial anaesthesia. The legs were immersed in water at 45°C. The usual general reaction followed and at 25 minutes, there was a profuse urticaria on the face, body, left arm, and thighs. The legs were withdrawn from the water at 26 minutes. At 27½ minutes the circulation was restored to the right arm. A bright reactive hyperaemia quickly spread over the arm equally on the anaesthetic and on the sensitive skin. At 29 minutes, wheals had appeared all over the previously occluded part of the right arm except on the anaesthetic area. At 32 minutes, the reactive hyperaemia began to pale on the anaesthetic area on which no flares, wheals, or red spots were seen. The eruption on the much flushed sensitive skin was as usual much more profuse than on the other arm, and specially at the site of the occluding cuff. At 41 minutes, the anaesthetic area was pale, unspotted, and unwhealed, and contrasted strikingly with the deeply flushed and much whealed surrounding skin. At 60 minutes, sensation had returned to the forearm but no urticaria had developed on the previously anaesthetic area, the eruption elsewhere had largely subsided.

We may accept, then, that the urticaria appearing in response to warming the legs is due to the release of H-substance in the skin through the peripheral nerves. Since arresting the circulation to the warmed limbs prevents the appearance of the urticaria, we conclude that the warm blood, returning from the limbs, stimulates some central mechanism (14). It seems reasonable to believe that the urticaria following exercise and emotion in these cases is due to a similar action through peripheral nerves induced centrally or reflexly. We shall now consider what efferent nerves are involved.

The nerves involved

Marchionini and Ottenstein (13) provoked the urticaria in their case by giving pilocarpine intramuscularly, Harris (5) induced an attack by giving pilocarpine combined with a hot air bath. We have found that pilocarpine given subcutaneously to Cases 1 and 2 provokes a general urticaria of the same type as that we have been describing. The injection of normal saline has no effect. To illustrate, Case 1 lay comfortably on a couch reading a book. The skin was free from urticaria. The chest was exposed, the rest of the body covered with a blanket. After 10 minutes, the skin remaining normal, 5 mg pilocarpine nitrate was injected into the right upper arm.

(zero time) At 6 minutes, a blotchy erythema appeared on the chest, neck and shoulders and sweat broke out on the upper lip. The erythema and sweating became general. At 15 minutes, very many minute wheals had appeared all over the body and the site of injection was covered with them. Itching was intense. As usual, the palms and soles did not itch and showed no wheals or red spots, the axillæ also, though sweating freely, were almost entirely free from rash, showing only a few scattered wheals and red spots. At 40 minutes, sweating had ceased and the urticaria was subsiding. Throughout, the patient made no complaint, on being questioned later, she said she had been quite comfortable and unalarmed, though surprised at the appearance of the rash under these circumstances. She had not felt sick, but her mouth had been noticed to water.

In this case and Cases 2 and 3,* we found that atropine almost abolished the urticaria in response to warming the legs. Thus in Case 1 the skin being free from wheals, 1.3 mg atropine sulphate was injected subcutaneously, the pulse rate was then 96 per minute. Half an hour later, when the pulse rate was 140, the mouth dry and the face flushed, the legs were immersed in water at 45°C (zero time). The body was covered with a blanket. After 15 minutes the patient felt very hot, but there was no obvious sweating and no whealing. During the next 15 minutes, a little sweat broke out on the body and a few scattered wheals developed, but neither sweat nor wheals appeared on the face. The feet were withdrawn after 30 minutes' warming, no more urticaria developed.

Pilocarpine nitrate, 0.5 per cent, introduced into the skin by electrophoresis provokes an urticaria limited to the area over which the electrode is applied (Cases 1, 2, 3, 4 and 6). For example, in Case 1, using a modification of the method described by Wayne (18), 0.5 per cent pilocarpine nitrate was ionised into the skin through a non-polarisable electrode applied to the skin of the forearm (anode area 4.3 sq cm, current 21 microamps, 8 volts). Itching began after the current had been passing for 2 minutes and a flare appeared on the skin around the electrode. When the electrode was removed after 10 minutes' passage of the current, the anode area was deeply flushed and surrounded by a flare, minute closely set wheals soon appeared in this area and covered it 4 minutes after the current was stopped. No wheals appeared outside this area. Under the same conditions, Ringer's solution alone had no effect on the skin of these patients, while neither Ringer's solution nor pilocarpine in this concentration had any effect on the skin of control subjects.

These observations suggest that the peripheral nerves involved belong to the parasympathetic system or, in Dale's terminology, are cholinergic nerves. Strong support for this suggestion is provided by the observation that the urticaria is also provoked by choline derivatives given subcutaneously or applied locally. Because of the uncertain action of acetylcholine given

* In Case 3 the urticaria appeared as the effect of atropine was passing off

subcutaneously, we have used instead carbaminoylcholine chloride ("doryl" Merck) in doses of 0.5 mg. For example, in Case 2, which had been lying comfortably covered with a blanket on a couch for some time, 0.5 mg doryl was injected into the left upper arm (zero time). At 1½ minutes, the face flushed, and this flush spread all over the body, at 2 minutes, the mouth began to water and at 3½, sweating broke out. At 6½ minutes, many wheals appeared on the face, neck, trunk and arms, and at 9 minutes, on the thighs and legs. She complained of much itching, of feeling sick and faint, and of mistiness in the eyes, she began to shiver. At 20 minutes, the urticaria was at its height, almost the whole body was covered with wheals which in places, specially the back, had become confluent over large areas. The palms and soles and the axillæ were unaffected, the axillæ being pale. At 30 minutes, the general symptoms were passing off, at 45 minutes, the eruption was subsiding. At 70 minutes, the patient felt normal and the urticaria had largely disappeared. Similar observations were made in Cases 4, 5 and 6. Acetylcholine, 0.2 per cent in Ringer's solution, introduced locally into the skin by electrophoresis, is uncertain in its action, only occasionally producing urticaria. Addition of 0.01 per cent eserine salicylate, which itself has no effect on the skin, causes whealing (Cases 2 and 3). Doryl, 0.05 per cent in Ringer's solution, also regularly provokes the local urticarial reaction (Cases 2, 3, 4, 5 and 6). For example, in Case 2, 0.05 per cent doryl was ionised into the skin of the right forearm for 10 minutes, using the same anode and current strength as for pilocarpine. Itching began and a flare appeared round the anode while the current was passing. On removing the anode, its area was flushed and beginning to wheal and was surrounded by a conspicuous flare. Seven minutes later, the area was covered with wheals, no wheals appeared outside it.

Acetylcholine with eserine, or doryl, so introduced into normal skins produce only a local reddening, lasting 10 to 15 minutes, without flare or wheal.

Viewed in the light of current physiological conceptions, these observations strongly suggest that the urticaria in our patients is due to the release of acetylcholine in the skin as a result of the stimulation of cholinergic nerve fibres. The release of acetylcholine in turn leads to the liberation of H-substance from skin cells.

So far we have not been able to determine the course pursued by these nerves from the centre to the periphery, whether they belong to the sensory or sympathetic groups. We have in mind the possibility of preventing the development of the urticaria on one part of the skin either by anaesthetising sympathetic ganglia by a paravertebral injection on one side or by paralysing sensory nerves with a low spinal anaesthetic, we have not yet had the opportunity of making these observations.* According to present knowledge,

* We have on two occasions in Case 2 attempted to block the sympathetic ganglia at the root of the neck by injecting procaine but without success. We have also noted urticaria of this type in a girl, aged 19, in whom a bilateral sympathectomy had been performed for severe acrocyanosis. This case, however was like Case 6 of our series, the urticarial attacks, provoked by warming for even an hour, were only slight and confined to the upper part of the trunk.

the nerves involved might belong to either group. The sympathetic fibres to the sweat glands are probably cholinergic as also probably are the sympathetic vasodilator fibres to the skin, for the existence of which there is some evidence in man (12). Again, the so-called antidromic stimulation of the sensory nerves leads to cutaneous vasodilatation which is attributed by Lewis and Marvin (11) to the release of a stable vasodilator substance, probably H-substance, in the skin, whether this substance is released directly or indirectly through the initial release of acetylcholine is unknown. Another example of cutaneous vasodilatation arising through stimulation of sensory nerve fibres is the flare (8), Dale (2) suggests that this dilatation is due to a release of acetylcholine from the effector endings of the nerve fibres.*

Although the anatomy of the nerves involved in these cases remains undetermined, our observations give no ground for believing that their activity is in any way abnormal. We have seen that the nerves are probably cholinergic, the choline derivatives, acetylcholine and doryl, provoke a local urticaria when introduced by electrophoresis in concentrations that do not provoke urticaria in normal subjects. It seems, therefore, that the skin of these patients responds abnormally to a normal release of acetylcholine at the nerve endings. Again, since pilocarpine is known to produce its effects on the skin after nerve degeneration, we must assume that the abnormality lies distally to the nerve endings. As we shall see later, an area of skin once whealed in response to nerve stimulation, is, for a time unresponsive not only to further nerve stimulation but to pilocarpine or doryl introduced. This unresponsive state again points to an abnormal condition of the skin cells. We may accept, then, that the abnormality in these cases lies in the skin and not in the nervous system.

We proceed to consider further observations.

Further observations

Effects of local blood flow on the urticaria. At one stage of our investigation, we had the idea that the urticaria might be due to some abnormality of the sweat,† and we thought that if the sweat were prevented from escaping freely from the ducts, it might more thoroughly permeate the epidermis and so increase whealing. We found in fact, that when an area of skin is painted with collodion before sweating is induced by warming the legs, then when the collodion is removed after warming is stopped, many more wheals develop on that area than on the surrounding skin or on the corresponding area on the other side of the body. The wheals are often so numerous that the site of the patch becomes completely whealed. For example, in Case 1, two patches of skin, about 4 cms square, were painted with collodion solution

* On many occasions in our cases we have provoked conspicuous flares on the skin by pricking in histamine and morphine and by faradism, we have never seen wheals develop in these flares.

† See Appendix, page 271.

When this was dry, the legs were immersed in water at 45°C (zero time) At 11 minutes, the patient was sweating freely and scattered wheals were appearing on the trunk and limbs At 17 minutes, conspicuous red flares, 2 cms wide, had developed, and persisted, around the collodion patches, between which and the reddened skin a few beads of sweat were confined At 30 minutes, warming was stopped and the patches removed, partly by stripping and partly by ether Many wheals quickly developed and, 10 minutes later, both areas of skin were completely whealed We have made this observation repeatedly on all our cases and with the same result, many more wheals appear on the site of the patch than on the surrounding skin, though they are not always so numerous as in this instance Other observations, however, lead us to attribute this result, not to the confinement of sweat, but in large part to a reduction of the blood flow preventing the removal or destruction of released substance The intensification of whealing does not seem to be due to adding a factor of injury to the nervous element responsible for the urticaria, the application and removal of collodion without warming the body does not wheal the skin None of our cases display urticaria factitia, we have firmly stroked the skin, before and at intervals during warming, without provoking whealing along the line of the stroke The collodion in drying contracts and draws the skin together, in one instance the dry collodion patch removed entire measured 20 by 30 mm, while the skin area on which it was painted measured 33 by 37 mm That it constricts the skin vessels is shown by the narrow zone of pallor that comes around it as it dries We estimate the constricting pressure exerted by the collodion to be of the order of 50 mm Hg For, on the one hand although the H-substance is released in the skin under the collodion patch, the wheals do not form until after its removal Lewis (7) showed that pressures of about 30 to 50 mm Hg are required to be applied to the skin to prevent wheals appearing On the other hand the pressure exerted by the collodion is insufficient to prevent the vessels dilating when H-substance is released, the zone of pallor is replaced by a flare and the skin beneath the patch becomes reddened According to Lewis and Haynal (7), the minimum values for the pressure in the minute vessels during a bright histamine flare are about 50 to 60 mm Hg In our cases, the pressure in the minute vessels is probably higher than this, because in addition to the pressure produced by the local vasodilatation due to H-substance release, there is also the extra pressure produced by the opening up of larger vessels through the inhibition of vasomotor tone in response to body warming Again, whealing is more profuse on the site of a cuff applied during body warming at a pressure of only 60 mm Hg, the wheals developing after the removal of the cuff We have also repeatedly seen intensification of whealing on any part of the body subjected to pressure while the legs are warmed, for example, whealing is more profuse where the patient has leaned against a chair, and where the skin has been pressed on by closely fitting clothing Moreover, if the local blood flow is reduced, not by pressure but by immersion in cold water,

20 to 25°C, there also wheals are more numerous. On the other hand, if the local circulation is greatly increased by immersion in hot water, whealing is abolished or very greatly reduced. The absence of whealing on heated parts has already been noted, usually no wheals form, but we have occasionally seen a few reduced wheals develop on a heated arm when the wheals are very profuse elsewhere. The difference between the whealing on an arm immersed in hot water and on one either immersed in cold water or to which the circulation is arrested is conspicuous. For example, in Case 1, the right arm was immersed in water at 25°C, the left arm and both legs were immersed in water at 45°C. The usual urticaria followed after a few minutes. A moderate eruption came on the body and arms down to the lines of immersion, none appeared on the warmed parts. Below the cold water line, the right arm became profusely whealed, many wheals came on the back of the hand and a few on the fingers. None appeared on the palms. After 30 minutes' warming, the limbs were withdrawn from the water. The patient then complained of an intense burning feeling in the right arm where the wheals had coalesced over large patches. The left arm and legs remained free from wheals. Immersion of the arm in cold water alone without warming the body, did not provoke whealing.

Lewis and Grant (8) have previously shown that if histamine is pricked into, or if H-substance is released in, skin to which the circulation is greatly increased, the subsequent whealing is either abolished or greatly reduced. They concluded that the substance introduced or liberated is washed away before it can act effectively on the vessels. They also showed that it is held *in situ* by circulatory arrest or cooling. The observations recorded above are in agreement with this.

In our cases we know that the release of acetylcholine precedes that of H-substance. The effect of blood flow on whealing may be due, therefore, to change of concentration of either acetylcholine or H-substance.

Effect of a previous attack. While the local state of the circulation is one of the chief factors modifying the urticarial response, another is the time interval since, and the severity of, the last attack of urticaria. Marchionini and Ottenstein (13) remarked in their case that repetition of the sweat baths seemed to lead to a lessening of the urticaria. In all our cases we have noted a very definite, though temporary diminution in the urticarial attacks when the stimuli are too frequently repeated. The diminution is the more conspicuous the greater the initial response for each individual. Thus, in the severe cases, slight attacks, in which only a few wheals develop, can be provoked repeatedly during the day. A moderate attack, induced for example by warming the legs for 20 to 30 minutes, can be provoked daily, but if the same warming is given in the morning and afternoon of the same day, the urticaria in the afternoon is less than that of the morning. A severe attack, in which most of the skin is whealed, such as is caused by warming the legs for an hour or by the subcutaneous injection of 0.5 mg doryl, can only be reproduced after an interval of about 2 days. For example,

in Case 1, an hour's warming provoked the severe attack already described on page 258. The same warming on the next day produced only a slight attack, on the third day very few wheals developed and on the fourth day these were confined to the upper part of the trunk, the head and limbs remaining unaffected. On repeating the warming a week later, a severe attack followed. The patient said that she had never before been so free from spots as during that week and that she had been able to take much more exercise without experiencing the rash. So also in Case 6, in which the attacks were never more than slight, warming for an hour on three successive days led to the almost complete disappearance of the urticaria, we found that the maximum response to warming, exercise or doryl, could be provoked only when he had avoided exercise and hot baths for the preceding two or three days.

So great is the diminution of the urticaria following an attack provoked by an hour's warming of the legs or by the subcutaneous injection of 0.5 mg doryl, that we have used this as a therapeutic measure, to give the patient a period of relief from the troublesome rash. For example, in Case 2, a severe attack was induced by warming for an hour. The next day this patient was able to dance throughout the evening which previously she had been unable to do on account of a profuse rash developing rapidly. Two days later, she skipped vigorously and, as usual, provoked a severe eruption. This patient now regularly provokes an attack by skipping before a dance.

This general diminution of the urticaria is, at least in part, an expression of the fact that any part of skin once whealed through the nerves, or by the general or local administration of doryl or pilocarpine, fails again to respond by whealing until after an interval of about two days. So that the more numerous the wheals provoked on an area of skin by any of these stimuli, the fewer are the wheals that will develop there in response to any, again applied within that period. Thus, where, in an attack induced by warming the legs, an area of full whealing occurs at the site of an occluding cuff or a collodion patch, that site shows little or no urticarial response either if the legs are again warmed and a cuff or collodion is re-applied, or if doryl or pilocarpine is introduced generally or locally within two days, the surrounding skin, not having been completely whealed, wheals more or less profusely, according to the degree of the initial response. On the other hand, where, as in the experiment described on page 261, an area has escaped whealing, that area, and that only undergoes profuse whealing subsequently.

The failure of an area to wheal again is not due to the vessels being refractory to histamine. After the original whealing has subsided, the area wheals as well as does the normal skin of a control subject to 1 in 10,000 histamine base pricked in. It is not due to lack of H-substance in the skin cells, for the skin wheals normally when injured, as by pricking in morphine. For example, in Case 2, an area of skin on the right upper arm was painted with collodion (to intensify whealing locally), and a moderate attack of urticaria was provoked by warming the legs. Whealing became full on the

collodion area, there were only scattered wheals on the surrounding skin. The next day, the skin being apparently normal, 1 in 10,000 histamine base and 0.1 per cent morphine tartrate were pricked, each at 3 spots, into the skin, both within and around the area which the day before had been covered by the collodion and fully whealed. Whealing was normal in all the pricked spots. Pilocarpine, 1 per cent, was then ionised into the skin outside the collodion area, and produced the usual whealing. Inside the collodion area, it provoked no obvious reaction. Moreover, refractoriness, as originally described by Lewis and Grant (8), involves only the absence of whealing in response to further histamine introduced or H-substance liberated, the local vasodilatation and the flare develop as usual. When whealing fails in our patients, as for example on rewarming on the day after a severe attack has been induced, the skin previously whealed, and now remaining unwhealed, is no more flushed than that of normal subjects similarly warmed. It seems, therefore, that recently whealed skin fails to wheal again because H-substance is no longer liberated. Further, this failure of H-substance to be liberated as usual, cannot be attributed to failure of acetylcholine to be released from the nerve endings, for H-substance is not liberated when doryl is introduced into the skin. We may say, therefore, that H-substance is not released because the skin cells have become unresponsive to acetylcholine. In support of this, it is to be pointed out that for the development of unresponsiveness it is unnecessary that whealing should take place. We have shown that when the urticaria is provoked by warming the limbs, little or no whealing occurs on the warmed parts, presumably because the released H-substance is removed too quickly to allow it to act on the vessels. But the skin of these warmed parts, when tested later, is found to be about as unresponsive as skin on which whealing has been profuse.

We must distinguish clearly between failure of whealing due to refractoriness and that due to unresponsiveness. *Refractoriness*, as originally described by Lewis and Grant (8) is a phenomenon of the vessels, it does not persist for long, there is a fairly prompt recovery. On the other hand, what we have called *unresponsiveness* applies to the skin cells, and persists for about two days. Both refractoriness and unresponsiveness can be displayed in our cases as follows. Thus, when the circulation to an arm is arrested while the legs are warmed for 20 to 30 minutes then, on release of the circulation, profuse whealing comes on the arm. If, however, the ischaemic arm is immersed in water as hot as can be borne, 40° to 43°C, while the legs are warmed, no wheals form when its circulation is restored after withdrawing the arm and legs from the hot water. This failure of whealing on the warmed and occluded arm is due to the vessels having become refractory. That H-substance has been released is shown by the numerous local red spots that become defined as the hyperaemia, due to the occlusion and warming, subsides. Thus refractoriness soon passes off, for full whealing follows when histamine or morphine is pricked into the skin of the arm as soon as the reddening has subsided. But when the legs are warmed then,

or the next day, or doryl injected subcutaneously, few or no wheals, flares or red spots develop, the skin remaining unresponsive

We have observed a similar condition of unresponsiveness of the skin in a colleague sensitive to pollen. On two occasions areas whealed by the intradermal injection of pollen extract gave much reduced whealing to this 24 hours later, though they whealed normally to histamine and morphine pricked in. According to present conceptions, this reduction of the urticarial response to pollen extract may be attributed to a temporary desensitisation of the skin cells. The first injection of pollen antigen uses up pollen antibody in the skin cells and time is required for the re-formation of new antibody. It is tempting to regard the unresponsiveness in our cases as being of a similar nature. We might say that the urticaria is due to the skin cells having acquired a sensitivity to acetylcholine and that when the cells once react with it this sensitivity is discharged and requires a period of about two days for its re-establishment. There is evidence that the unresponsiveness is to some extent specific for the stimulus provoking it. Thus we found that Case 4 of our series suffered not only from the urticaria of the type we have been describing, but also from an urticaria in response to cold. We were led to test the effect of cold on her skin by several unusual features in her case. She had on one occasion suffered from swelling of the lips on eating ice cream. She was certain that her worst attacks were experienced when sea bathing, although she was not taking vigorous exercise. On leaving the hospital after a severe attack had been induced by warming the legs, she found that the rash recurred on her face on going out into the cold wind. She stated that she had often noticed the rash develop on parts exposed to cold. We found that the application to the skin of water at a temperature of 15°C for 5 minutes caused almost the whole area to wheal*. We found further, that though a severe attack induced by warming the legs rendered the skin unresponsive to further warming or to doryl, the skin still whealed fully to cold. Also, skin whealed by the application of cold did not become unresponsive to further cold. The same area retested by cold 2½ hours later, when the original whealing had subsided whealed again fully. This lack of unresponsiveness to cold agrees with the previous observations of Harris, Lewis and Vaughan (6). It is clear that in regard to unresponsiveness the two types of urticaria are distinct. We have examined a case of urticaria factitia from this point of view and we find that an area whealed by stroking the skin wheals again fully when stroked as soon as the original wheal has subsided. Blum, Allington and West (1) find that in a case of urticaria due to light, repeated stimulation of the skin does not seem to lead to a lessening of the urticaria. Further observations on unresponsiveness are required. We may say, however, that we regard the interchangeability of nervous activity and a choline derivative, doryl, to

* Note that Case 3 also gave a history of having suffered for a time from swelling of the face on going out into the cold. Neither this nor the other cases of our series showed whealing of the skin immersed in cold water or cooled by contact with ice.

provoke and display unresponsiveness, as further evidence that the urticarial attacks in our cases are due to the stimulation of cholinergic nerves

Discussion

From what has been said in the preceding pages, it will be realised that when the cholinergic nerves are stimulated to activity, the urticarial response depends on several factors. It depends on the distribution and degree of the nervous activity, or in other words, on the site and amount of the acetylcholine released in the skin. It depends on the time since, and the severity of, the last attack of urticaria for this, by modifying the responsiveness of the skin cells, affects the amount of H-substance released. It depends also on the local state of the circulation, for this modifies the effect of liberated H-substance on the vessels. There is, however, at least one other factor, and this, for want of clearer understanding, we may describe as the distribution and degree of the sensitivity acquired by the skin cells to the products of nervous activity. Thus, in our severe cases, even prolonged warming or strenuous exercise fails to provoke urticaria in the axillæ or on the palms and soles, while it is always sparse on the backs of the hands and feet. This cannot be attributed to absence or sparseness of the nerve supply in these parts, for it happens also when doryl is injected subcutaneously. It must depend, therefore, on some factor in the skin. In the case of the axillæ, this factor may be that H-substance here released does not show itself as a frank urticaria, for 1 in 10,000 histamine base pricked into the epilated axillæ provokes very little recognisable whealing or reddening. In the palms and soles, however, though whealing to histamine is barely recognisable, local red spots can be seen and itching is considerable. We know, also, that in other types of so-called spontaneous urticaria, whealing of the palms and soles frequently occurs and itching is often a troublesome feature. During urticarial attacks we have never witnessed whealing or local red spots develop in the palms of our cases and none has ever experienced itching here. Moreover, in Case 6, the sensitivity of the skin seems to be confined to the trunk. Urticaria never develops on the arms or thighs in response to warming the legs or to exercise, even when collodion patches are applied. It also fails in these regions when doryl is injected subcutaneously or introduced locally by electrophoresis. Further, the urticaria on the trunk is never so profuse as in the other cases, even when collodion is applied or doryl locally introduced. We may say, then, that this case displays a sensitivity not only more localised but also less in degree than that of the other cases. Case 3 is intermediate between No. 6 and the remaining 4 cases.*

* *Note added in proof stage (June, 1936)* We have since observed five other cases (four females and one male, whose ages range from 17 to 34), so that this type of urticaria is not uncommon. One of the cases, a girl of 21 years, is unusual in that flares and wheals, accompanied by itching, develop on the palms of the hands in response to warming the body, this case also displays mild factitious urticaria.

SUMMARY AND CONCLUSIONS

- 1 A group of six cases is described showing a very characteristic type of urticaria
- 2 The urticaria is provoked through efferent peripheral nerves when these are stimulated by emotion, by exercise, or by warming the body
- 3 The efferent nerves are very probably cholinergic, since the urticaria can be provoked also by the local or general administration of pilocarpine or choline derivatives. The anatomical distribution of these nerves is undetermined
- 4 The abnormality in these cases lies in the skin and not in the nervous system
- 5 There is no evidence that the sweat glands are concerned
- 6 A condition of unresponsiveness of the skin cells is described and is to be distinguished from refractoriness of the vessels

OBSERVATIONS ON SWEATING

We have already noted that Marchionini and Ottenstein (13) attributed the urticaria, at least in part, to sensitivity of their patient's skin to sweat. They found that her skin, when scarified, gave a positive reaction to her own and a normal subject's "ekrine" sweat, applied as a patch test, it reacted hardly at all to "apocrine" sweat, thus apparently accounting for the absence of urticaria from the axillae. Normal skin gave no reaction. It is to be remembered that in our cases, not only the axillae, but also the palms and soles are spared, whealing is sparse on the backs of the hands and feet, fingers and toes. This distribution cannot be accounted for by what is known of the anatomical distribution of the different kinds of sweat glands, though the apocrine glands are apparently confined to special areas including the axillae and the pubic region, we cannot find it stated that the ekline glands are there absent or much reduced in number, many ekline glands are present in the palms and soles. Apart from these special regions, there does not seem to be any close relation between the outbreak of sweat and the development of whealing. At one time the urticaria may be well developed before sweating is profuse, at another the reverse may be found, whealing does not occur over every active gland. These last observations do not, however, exclude a relationship between sweating and the urticaria, the discrepancies might be accounted for by local factors other than distribution of sweat glands, by differences of local blood flow, or previous whealing not recovered from. Again, we have not observed sweating to occur in areas whealed by the local application of doryl or pilocarpine, even when as sometimes happens, there is an interval of 5 to 15 minutes between the removal of the electrode and the beginning of whealing. There is no obvious sweating on an arm rendered ischemic or after its circulation is restored, yet whealing is profuse.

In view, however, of the findings of Marchionini and Ottenstein (13) we have made observations on the sweat of ourselves (R B P and R T G) and of Cases 1, 2 and 3. In these observations sweating was induced by warming the legs and sweat was collected in two ways. Successive small samples from one part were obtained by scraping the rim of a beaker against the sweating skin, the subject being enclosed in a tent to lessen evaporation. Larger quantities were obtained by enclosing the arms and body from neck to waist in a waterproof jacket provided with an outlet, the jacket being loosely drawn together at the neck and closed round the waist by a rubber bandage. The reaction of the sweat samples was estimated by the capillator method (British Drug Houses, Ltd).

According to Whitehouse (19), the reaction of sweat as secreted from the glands is slightly alkaline, the ordinary acid reaction being due to substances given off from the general surface of the epidermis. We have confirmed his observation that if the skin is well washed with distilled water before sweating is induced, the reaction of the sweat is slightly alkaline (pH 7.3 to 7.5). We have found further that when without previously washing the skin, successive samples are collected from one part the reaction of the samples changes from acid to alkaline as sweating continues. Thus, in one control subject, the reaction of sweat from the forehead was 5.3 in the first sample taken as sweating broke out. In subsequent samples it became progressively less acid until in the last, taken after 20 minutes sweating, the reaction was 7.5. The sweat so collected is turbid from epidermal debris, this turbidity is removed, in great part by filtering

through paper, and entirely by passing the sweat through a Seitz bacterial filter. We have repeatedly injected 0.02 c.c. of samples of sweat intradermally into our patients and ourselves, the sweat being filtered and unfiltered, undiluted or diluted with either normal saline or buffer phosphate solution, and injected as soon as collected or after intervals up to 4 days, the samples being kept in a refrigerator. The degree of the skin reaction to injected sweat, we have estimated from the diameter of the flare and the increase in the diameter of the wheal, measured at the height of the reaction. In this way, we have obtained no indication that the sweat of the 3 patients differs from our own or that our patients' skins are unusually sensitive to their own or to our sweat. The reaction of the sweat, its filtration, and the time interval between its collection and injection makes no material difference in the reactions observed in our patients or ourselves. There is no difference between the sweat collected from a patient in whom the skin is responsive, and unresponsive. Washing one half of our patient's skin beforehand, to remove the acid cloak, has not altered the subsequent urticaria, the wheals being as profuse on the washed as on the unwashed side. While there have been slight variations from time to time, the reactions of any one of the 5 individuals to intradermal injection has been the same to sweat from that individual and from any of the others; the reactions of Case 2 have been greater than those of Cases 1 and 3 and the reactions of R T G greater than those of R B P, those of Cases 1 and 3 were equal to those of R B P and those of Case 2 to those of R T G. Undiluted sweat provoked little or no reaction in Cases 1 and 3 and R B P, in both Case 2 and R T G it provoked flares of about 50 mm diameter and an increase of wheal size of 3 mm, 1 in 10 dilutions sometimes caused smaller reactions while 1 in 50 dilutions caused none. In all subjects, unfiltered and undiluted sweat leaves an area of redness, tenderness and swelling, persisting for several days, due probably to its content of debris and bacteria, with Seitz filtered sweat, only a red spot remains for 24 to 48 hours after the subsidence of the initial wheal.

These observations provide no evidence that the urticaria in our cases is due to either an abnormal quality of their sweat or to an abnormal sensitivity of their skins to normal sweat. On the one occasion on which we tested it, there was no difference between the effect of sweat collected from the axillæ and the back. It is to be remarked that if our observations had been confined to one case, Case 2, and one control subject, R B P, the greater skin reactions of Case 2 might have led us to a different conclusion. If there is an intermediate link in the chain of events between the release of acetylcholine from the nerve endings and the liberation of H substance from the skin cells, we have no evidence that this link is activity of the sweat glands.

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OBSERVATIONS RELATING TO THE INNERVATION OF THE SWEAT GLANDS OF THE FACE

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IN a previous publication (14) I reported observations on sweat secretion in man with reference to the action of pilocarpine and the innervation of the sweat glands. The observations appeared to furnish evidence against the belief that the human sweat glands have a double innervation. Further investigation, however, has brought to light some facts which point to a different conclusion, as regards at least the sweat glands of the face. The investigation is recorded in this paper.

For an account of the literature on the nerve supply to the sweat glands reference should be made to the monograph of Kuno (9). I have previously (14) reviewed briefly the evidence relating to the belief that in man the sweat glands have a double innervation. A further account may be inserted here.

The sweat glands are supplied by secretory fibres which run in the sympathetic division, or thoracico-lumbar outflow, of the autonomic nervous system. It is established beyond doubt that when the sweat centres are stimulated by heat or exercise the efferent impulses travel by the sympathetic secretory fibres, and by these fibres only. The same probably holds for emotional stimulation. The evidence for a second, or "parasympathetic," set of fibres to the sweat glands has not up to the present time been convincing. The evidence consists of two main parts: (a) the action of pilocarpine, and (b) the effects of injecting drugs into the cerebral ventricles.

After the sympathetic nerves to an area have degenerated the area may still sweat in response to pilocarpine, and, in fact, the response is sometimes excessive. After, however, degeneration has occurred of a mixed peripheral nerve, *e g*, a nerve of a limb, pilocarpine fails to produce sweating in the area of distribution of the nerve (8). The conclusion has therefore been drawn, despite the evidence to the contrary from animal experiment (1, 10), that in a mixed peripheral nerve there are some secretory fibres.

* In receipt of a part time grant from the Medical Research Council. The cases described in this report were all under the charge of Mr N M Dott. I am indebted to him and to Professor D Murray Lyon for the facilities for this investigation, and to Sir Henry Dale for helpful criticism.

(other than the sympathetic fibres) on the integrity of which the action of pilocarpine depends. The evidence is, however, unsatisfactory. I have shown (14) that in man pilocarpine may cause sweating on the face after degeneration of all types of nerves to this area, and that, therefore, pilocarpine must act directly on the sweat glands.

The second piece of evidence is derived from observations by Cushing (2). He found that when generalised sweating was produced by intraventricular injection of pituitrin or pilocarpine, an area of skin on the face and scalp, to which the sensory nerves had been divided by a previous operative incision, remained dry. Assuming that the sympathetic secretory fibres were distributed with the blood vessels, and that they were intact in the area which remained dry, he suggested that the impulses from the cerebral centre which had been stimulated by intraventricular injection must be conducted along antidromic fibres in the sensory nerves. As will be recorded later, I have established that the sympathetic secretory fibres are distributed with the peripheral branches of the trigeminal nerve. They would not, therefore, be intact in the anæsthetic area mentioned by Cushing. Again the evidence for an accessory nerve supply to the sweat glands is unsatisfactory.

Nevertheless there is an observation by Guttman (8) which suggests strongly a double nerve supply to the glands of the face. His subject was a man in whom the cervical sympathetic trunk had been severed. When the subject tasted vinegar, slight but definite sweating appeared immediately in some parts of the sympathetic denervated area. As will be recorded later, the observation has been confirmed and studied.

I—The distribution of the sympathetic secretory fibres to the sweat glands of the face

In the previous paper I showed that the sympathetic secretory fibres to the face were not contained in the extracranial portion of the facial nerve, nor were they severed in the sensory root of the trigeminal nerve. An inconclusive observation was also reported which might suggest that they were distributed with the peripheral branches of the trigeminal nerve. This fact has now been established.

Methods. The integrity of the sympathetic secretory fibres to an area which normally sweats readily can be tested by warming the body, while protecting the area to be examined from the direct action of heat. The area chosen was the forehead. The test was applied before and after division of the supraorbital nerve, and also after degeneration of the nerve. The response to pilocarpine was also examined. Three cases were investigated in which the nerve was resected while injury to the accompanying vessels was avoided. The results were substantially the same in all cases. One case will be quoted in detail.

Case 1. Female, aged 42 years, a case of left supraorbital neuralgia. No feature of importance was elicited from examination of the nervous system.

Before operation the sweating and flushing responses to warming the body were equal and simultaneous on both sides of the face. Subcutaneous injection of pilocarpine (12 mg) also induced symmetrical sweating and flushing.

First operation Anæsthesia—Omnopon gr $\frac{1}{2}$ subcutaneously, followed by Avertin per rectum. No atropine or ether was administered.

No spontaneous sweating was observed during the operation. At the supraorbital notch two diverging nerve trunks were exposed which appeared to be two main divisions of the supraorbital nerve. The nerves were severed, and the distal ends isolated and stimulated by a tetanizing current for about 15 seconds. Sweating appeared over the forehead at 7 seconds in areas corresponding to the course of each nerve. The supraorbital vessels were stimulated for one minute without causing sweating. The operation was completed by resecting portions of the nerves.

Examination at 24 hours. Fig 1 shows the sensory changes. Two areas of anæsthesia were separated by an area with retained sensation.

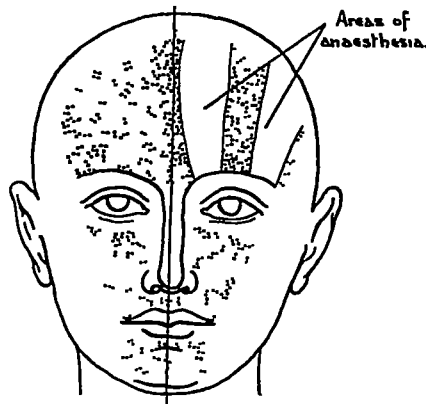


Fig 1 Case 1 Response to heat at 24 hours after first operation. Sweating areas stippled.

Evidently one branch had escaped detection. In response to heating the anæsthetic areas remained pale and dry, while the innervated areas showed flushing and sweating.

Examination at 21 days (after nerve degeneration). The conditions were the same as at 24 hours except that the anæsthetic areas had become slightly narrower. In response to heating the anæsthetic areas remained pale and dry. In response to pilocarpine (12 mg) sweating appeared over the entire left forehead, the sweating response in the anæsthetic areas was diminished, while the flushing response there was more intense than elsewhere.

Second operation The main trunk of the supraorbital nerve was exposed in the orbit, isolated from the accompanying vessels and resected.

Examination 3 days later. Anaesthesia was present over the entire distribution of the nerve. In the anaesthetic area there was no flushing or sweating in response to heat.

Examination 4 weeks later (after nerve degeneration). The conditions were the same as at 3 days. The anaesthetic area remained pale and dry during heating. Subcutaneous injection of pilocarpine (12 mg) produced sweating and flushing over the entire anaesthetic area. While the sweating response was delayed and greatly diminished in the area, the flushing response was more marked than elsewhere. In fact the anaesthetic area was clearly defined by its pallor during heating, and equally by its flush after pilocarpine.

Comment. The presence of sweat fibres in the trigeminal branches and the absence of sweat fibres in the peri-arterial nerves were proved by electrical stimulation. From the responses to heating we have proof also that the sympathetic secretory fibres to the sweat glands of the face are distributed with the peripheral branches of the trigeminal nerve. There is additional evidence which enables us further to trace their course. As already mentioned, they are not severed in the sensory root of the 5th nerve. Guttman (8) has reported that destruction of the Gasserian ganglion by carcinoma metastases, and also intracranial section of the 2nd and 3rd divisions of the trigeminal, did not alter the sweating response to heat. Evidently, therefore, the sympathetic secretory fibres join the branches of the trigeminal nerve outside the skull from the carotid plexus, in which they travel after leaving the superior cervical sympathetic ganglion.

The responses to pilocarpine after nerve degeneration confirm previous observations and support the view that pilocarpine acts directly on the sweat glands. Moreover, they indicate that the sudorific action of pilocarpine is not directly related to its vasodilator action. In this case flushing was intense in the area of nerve degeneration, while sweating was delayed and diminished.

II—*Sweating on the face during eating in an area with intact sympathetic secretory fibres*

Case 2. Male, aged 40 years, a case of syringomyelia. Symptoms had been present for about five years. Examination showed disturbance of pain and temperature sensation as high as the third cervical nerve, but no sensory abnormality in the face, and no sign of sympathetic paralysis or paresis.

Sweating. Sweating during eating had been present for about 5 years.

During the investigation it was found that slight spontaneous sweating was present almost constantly over the left side of the face, particularly on the forehead. Mild apprehension, such as was occasioned by any procedure employed for investigation, usually caused a slight increase of sweating in this area. Mild exercise had the same effect. The skin vessels over the left forehead were slightly dilated.

The stimulus Owing to the constant spontaneous sweating it was difficult to determine exactly the onset and duration of a response to stimulation. Sweating invariably increased during eating and involved the left side of the face in the usual distribution, namely, the forehead, temple, infraorbital region, side of nose and upper and lower lips. The most marked response was on the forehead. During a large meal the patient frequently mopped his face to prevent the sweat running down, and the left side of the scalp became wet with sweat as far back as the parietal region. Any stimulus to salivation produced sweating, even chewing a wad of wool or smoking a pipe or cigarette. Chewing movements were not in themselves effective, on the other hand, weak acetic acid in the mouth without chewing movements caused a marked response. With a strong, or prolonged, stimulus a lesser degree of sweating appeared over the medial part of the right forehead, and in the right infraorbital region (Fig 2). Sweating was always accompanied

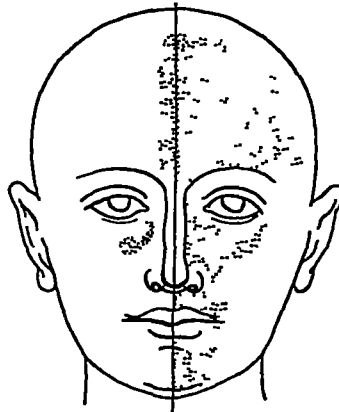


Fig 2 Case 2 Sweating response during eating Sweating areas stippled

by a slight, though definite, flush in the same distribution. Eating a piece of orange was the usual stimulus employed, active sweating appeared in 20 to 40 seconds and lasted for about 2 or 3 minutes.

Effect of adrenaline on the response to stimulation A small quantity (0.25 cc) of adrenaline injected subcutaneously produced no definite effect beyond a slight increase in pulse rate (52 to 62 per minute). No pallor was noted. Spontaneous sweating ceased at 2 minutes. At 4 minutes, when the effect on the pulse was definite, the patient ate a piece of orange, at 6 minutes a few tiny scattered beads appeared over the left forehead. Adrenaline thus had a strong inhibiting effect.

Effect of atropine on the response to stimulation After 1 mg atropine, injected subcutaneously, spontaneous sweating ceased at 8 minutes. The stimulus of eating was applied at 25 minutes, 35 minutes, 2 hours and 5 hours

after atropine without causing sweating. A slight flush was evoked on each occasion. The usual response reappeared at 10 hours.

Effect on nerve block on the response to stimulation. In all the experiments of nerve block recorded in this paper 1 per cent novocain solution, without adrenaline, was employed.

(1) The left supraorbital nerve was blocked with 5 c.c. of novocain. Sensation to pin-prick and spontaneous sweating disappeared simultaneously in the distribution of the nerve. A stimulus by eating invoked sweating in the usual distribution *except in the anaesthetic area*.

(2) The left sympathetic trunk was blocked at the root of the neck by 20 c.c. of novocain. At 5 minutes a well-marked Horner's syndrome was observed, and shortly afterwards all the signs of sympathetic paralysis of the left side of head and neck and of the left upper extremity. At 10 minutes a stimulus by eating was applied. The left side of the face remained dry, while definite sweating appeared over the right infraorbital region and medial part of the right forehead, which in this test served as control areas. The usual response was again obtained at 35 minutes when the signs of nerve paralysis had receded.

Response to heat. Over the left side of the face sweating soon became drenching when the body was warmed, and sweating was accompanied by a well-marked flushing. By contrast the right side of the face showed a response in flushing and sweating which was very slight and certainly below normal.

Response to pilocarpine. The sweating response to 5 mg. of pilocarpine injected subcutaneously was unusually prompt (4 minutes) and profuse. The response on the right side of the face was somewhat earlier and, for about 10 minutes, greater than that on the left side. Ultimately sweating was equal on both sides.

Response to a choline ester. 5 mg. of acetyl- β -methyl choline was injected subcutaneously. Flushing appeared at 70 seconds, first over the left side of the face, then involving the "blush" area. Sweating appeared, at 2 minutes, first and most profusely over the left side of the face.

Operation. The left superior cervical sympathetic ganglion was excised. The results confirmed those of sympathetic nerve block. At 24 hours a stimulus by eating produced sweating over the areas usually affected on the right side of the face, while the left side remained dry. On the 7th day the response to heat was tested. The area of sympathetic paralysis remained dry. As before operation the response on the right side of the face was very slight, though heating was continued till the sweating on the trunk was drenching and discomfort became almost intolerable. On the 8th day 5 mg. of pilocarpine was injected subcutaneously, sweating on the right side of the face was, as before operation, early and profuse. On the left side it was delayed and slight.

Re-examination was carried out 4 months after operation, the results are discussed in a later section.

Comment The sweat glands of the left side of the face reacted excessively to central stimulation, for example, in response to heat or emotion. They were hypersensitive to the action of a choline ester, and gave a well-marked response to a small quantity of pilocarpine. In addition they reacted to any stimulus causing salivation. This sweating during eating was obviously produced by nerve impulses, and not by a circulating hormone, since the response could be inhibited over a localized area by nerve block. The mechanism was clearly a nerve-reflex. The afferent impulses passed by sensory nerves from the mouth while the efferent fibres were contained in the peripheral branches of the trigeminal nerve. The effect of sympathetic paralysis, produced by novocain block or superior cervical ganglionectomy, on the response to stimulation proved that the efferent fibres were the sympathetic secretory fibres. Atropine, as might be expected, inhibited the response completely, the effect was of surprisingly long duration. The partial inhibitory effect of adrenaline may be noted. The effect of sympathectomy was to diminish the response to pilocarpine of the sweat glands in the affected area.

The reactions of the glands on the right side of the face were curious. These glands were abnormally sensitive to pilocarpine and abnormally insensitive to central stimulation by heating.

III—*Sweating during eating in an area of sympathetic paralysis*

Case 3 Male, aged 40 years. Following application of radium for angioma of the tongue the patient had developed intractable neuritis of the trigeminal and glossopharyngeal nerves on the right side.

On this account the sensory root of the trigeminal nerve had been sectioned 4 years previously, and a few months later an extracranial portion of the glossopharyngeal nerve had been resected. Subsequently superficial ulceration of the skin in the anæsthetic areas and corneal ulceration in the right eye had proved troublesome. These conditions were cured by excision of the right superior cervical sympathetic ganglion, the operation was carried out 2 years after that on the trigeminal root. It is assumed throughout that the post-ganglionic fibres to the sweat glands of the face in man arise in the superior cervical ganglion. About 10 days after ganglionectomy the patient noticed that sweating over the right side of the face occurred during eating. This phenomenon had persisted till the time of examination.

Examination revealed complete anæsthesia in the distribution of the right trigeminal nerve, signs of regeneration of the right glossopharyngeal nerve, and signs of sympathetic paralysis of the right side of the face.

Stimulus As in Case 2 sweating occurred following any stimulus to salivation. It was confined to the right side of the face, affecting mainly the forehead and to a less extent the infraorbital region and side of the nose (Fig 3). The most convenient stimulus was weak acetic acid in the mouth.

The test was carried out in the same way on each occasion. The patient retained the acid in the mouth for 15 seconds, then spat it out and washed out the mouth once with water. To this stimulus sweating appeared between 10 and 20 seconds and lasted for about 2 minutes. It was profuse over the right forehead and slight in the remaining areas. There was no obvious flush.

Effect of adrenaline on the response to stimulation 0.2 c.c. adrenaline was injected subcutaneously. There was no change in the pulse rate. The only effect was a well-marked pallor in the sympathetic-denervated area. At 5 minutes the stimulus was given. The response was slightly less than normal.

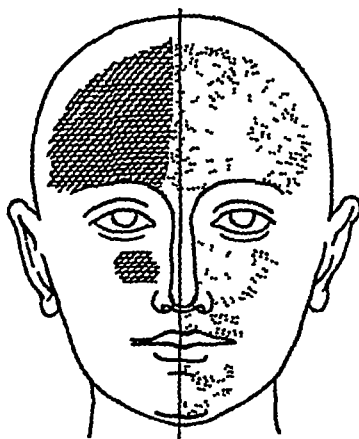


Fig 3 Case 3 Sweating response during eating cross patched Sweating in response to heat stippled

Effect of atropine on the response to stimulation 1 mg. of atropine injected subcutaneously annulled the sweating response completely.

Effect of nerve paralysis on the response to stimulation 2 c.c. of novocain was injected into and below the right supraorbital notch. One could be certain that the region of the supraorbital nerve had been thoroughly infiltrated, although, as the area was already anaesthetic, no means of testing the nerve block was available. There was no possibility in this injection of paralysing branches of the facial nerve. The usual stimulus was administered at 10 minutes, 15 minutes and 22 minutes. On each occasion the skin in the distribution of the right supraorbital nerve remained perfectly dry, while sweating occurred in the remaining areas usually affected.

Response to heat In this test the left side of the face sweated freely, while the right side remained pale and dry. The distribution of sweating is shown in Fig 3. It may be noted that there is an overlap of secretory supply at the root of the nose and over a thin strip of the right forehead near the middle line. This area of overlap was not involved in sweating of the right side of face during eating.

Response to pilocarpine After 15 mg of pilocarpine, injected subcutaneously, the response in the area of sympathetic degeneration was early, excessive and prolonged as compared with the left side

Comment As in Case 2 the sweat glands over a limited area of the face responded to any stimulus causing salivation. The effect of nerve block on the response to this stimulation was proof that sweating was caused by nerve stimulation and not by a circulating hormone. Again the mechanism was a nerve-reflex and the afferent impulses were carried by sensory fibres from the mouth for which in this case the nerves on the left side were available. The efferent fibres were contained in the peripheral branches of the trigeminal nerve. In this case, however, the efferent fibres were not the sympathetic secretory fibres, as these had long since degenerated, as stated there was no sweat response of the affected side of the face to body warming. Thus we have proof in this man of an alternative nerve supply to the sweat glands of the face.

On the right side of the face the sweat glands were hypersensitive to pilocarpine and the blood vessels of the skin to adrenaline. This is a property which is sometimes acquired by tissues to which sympathetic nerves have been divided.

The action of atropine is strong evidence that the efferent fibres involved in reflex sweating are cholinergic. Experimental proof that the sympathetic secretory fibres are cholinergic has been furnished by Dale and Feldberg (4).

Case 4 Male, aged 41 years. The left superior cervical ganglion had been excised 18 months previously for a condition of corneal ulceration.

Examination The test of warming the body confirmed the sympathetic paralysis of the left side of the face. Sweating on eating was not ordinarily observed. When the test of acid in the mouth was applied a few tiny beads appeared on the left upper lip and along the left eyebrow, i.e., in the sympathetic-denervated area. Attempts to augment the response by eserine were not notably successful. 1 mg eserine injected subcutaneously produced a very slight augmentation of the response to stimulation. A further 0.5 mg, however, caused nausea, distress and generalised sweating in which the sympathectomized area remained dry. This sweating was obviously of central origin and may have been due to stimulation of the sweat centre by eserine, or to a secondary effect of nausea, or to both. The observation suggests that the "cold" sweating of nausea, fainting and shocklike conditions is of central origin, and that the efferent fibres are the ordinary sympathetic fibres. In this case 15 mg of pilocarpine produced a response in the sympathetic-denervated area less than that in normally innervated areas.

Comment In a second case with degeneration of sympathetic fibres to the face reflex sweating was demonstrated in the sympathectomized area. The response, however, was very slight even after a strong stimulus. The lessened response to pilocarpine in the sympathetic-denervated area should be noted.

Case 2 re-examined at 4 months after the operation of left superior cervical ganglionectomy, when the sympathetic nerves to the left side of the face had degenerated

Since operation slight sweating continued to appear during eating over the right side of the face in the same limited area which was previously affected. He had not observed sweating on the left side of the face since operation.

There was no change of note in the sensory disturbance from the condition at the 8th day.

A stimulus of acid in the mouth produced slight sweating over the right side of the face in the areas which reacted to this stimulus before operation. In addition, however, some tiny scattered beads appeared over the *left* forehead in the sympathetic-denervated area.

The sweating response to 5 mg of pilocarpine was very similar to that on the 8th day, it was greatly diminished in the area of sympathetic degeneration.

Comment Again sweating during eating occurred in an area of sympathetic nerve degeneration. The sweating produced in this area by pilocarpine was less than in corresponding areas with sympathetic nerves intact.

In another case which was examined 4 months after superior and middle cervical ganglionectomy no reflex sweating could be induced. The same result was obtained from tests on several cases after cervico-dorsal sympathectomy in which only preganglionic fibres to the face were divided and no degeneration followed.

DISCUSSION

Four examples of sweating on the face during eating have been described. In two instances, Case 2 (after operation) and Case 4, the sweating was so slight that a complete study was impossible. The phenomenon was, however, *investigated in Case 2 (before operation) and in Case 3 in whom the response was excessive*. Sweating during eating was proved to be a result of reflex action and could be induced by any stimulus which would provoke salivation. It was impracticable, by interrupting the reflex arc on the afferent side, to determine the afferent pathways, which were evidently those of the salivary reflex. The efferent pathway was, in Case 2, the sympathetic secretory fibres, in Case 3 some fibres other than the sympathetic. It is very probable, though proof was not obtained, that sweating during eating in Case 2 (after operation) and Case 4 was also a reflex phenomenon and that the efferent pathway was the same as in Case 3, because in these instances the response involved only areas of sympathetic nerve degeneration.

Regarding the nature and origin of the alternative secretory fibres there are three possibilities. The first is that they are sweat fibres which are normally distributed to the face. The second is that they are secretory fibres normally supplying some gland, such as a salivary gland, and that, having been interrupted by previous injury, they have through faulty

regeneration grown to the skin and come to supply the sweat glands. The third possibility is that of a reflex through the Gasserian ganglion. For example, in Case 3 the afferent impulses might have passed from the mouth to the right Gasserian ganglion, there to be relayed to the face along sweat fibres in the right trigeminal. No reflex of this type is, however, known to physiology and the explanation need not be considered further.

The possibility of faulty regeneration of other secretory fibres is an explanation which has been suggested (6) for the "auriculo-temporal syndrome," which is that of sweating during eating localized to the region of the parotid gland. It must be considered in Case 3. Operation on the sensory root of the trigeminal may have involved injury to nerves, such as the greater superficial petrosal, which contain parasympathetic secretory fibres, and since, as Dale (3) points out, cholinergic fibres can always replace cholinergic fibres, it is highly probable that parasympathetic fibres, whether preganglionic or postganglionic, to any gland could replace the cholinergic sympathetic sweat fibres. The explanation is not, however, tenable for Case 2 (after operation) and Case 4, where the operative procedure was limited to removal of the superior cervical ganglion. Thus it seems reasonable to conclude that the fibres conducting the efferent impulses for reflex sweating after sympathectomy are sweat fibres normally present in the face. There is little information available regarding their course. The fibres presumably arise in the brain stem, they are distributed with the peripheral trigeminal branches which they must join somewhere distal to the sensory root. (This root had been severed in Case 3). Guttman (8) believes that sweat fibres travel in the facial nerve and join the trigeminal branches by peripheral communications. Such a course for the fibres under consideration is very improbable because the nerve block which inhibited sweating in the distribution of the supraorbital nerve (Case 3) could not have interrupted peripheral communications with the facial nerve. If sweat fibres are present in the facial nerve, they are probably confined to the intracranial portion.

It has been pointed out that the sympathetic sweat fibres as well as the alternative fibres are cholinergic. It seems accordingly inadvisable to label the alternative fibres as "parasympathetic," although the description is anatomically correct. I shall refer to them as "accessory" secretory fibres.

It has been shown, therefore, that sweating on the face during eating can be the result of a reflex with two possible efferent pathways. Under what conditions, physiological or pathological, is it invoked in man? Symmetrical sweating on the face during eating occurs, to a slight degree, in some apparently normal individuals, especially when they partake of spicy foods, such as curries, in a few the sweating may be somewhat profuse, as in the frequently-quoted instance of Brown-Séquard. In this form the phenomenon may be regarded as physiological. There is no direct evidence available regarding the mechanism, almost certainly, however, it is also reflex. Further investigation is necessary to decide which of the two available routes is taken by the efferent impulses.

Sweating on the face during eating may be localized and then frequently is excessive. This form, which is to be classified as pathological, is always preceded by injury to the nerves of the affected area. Most commonly it affects the region of the parotid gland—the “auriculo-temporal syndrome”—which has already been mentioned, exceptionally it occurs elsewhere (13). The syndrome is at present under investigation, and no further reference will be made to it in this paper. It will suffice to discuss the phenomenon of sweating during eating as it appeared in the cases reported here.

A common mechanism of reflex sweating has been presumed for Cases 3, 4 and 2 (after operation). The efferent impulses were carried by the accessory fibres and the response was confined to the area of sympathetic nerve degeneration. Reflex sweating was inhibited by the presence of intact sympathetic fibres, a similar inhibition by undegenerated post-ganglionic sympathetic fibres was shown also in the cases of cervico-dorsal sympathectomy. No case has been found of definite functional activity of the accessory fibres in the presence of intact or undegenerated sympathetic fibres. It is, therefore, possible that the accessory fibres play no important role in the sweating reactions of normal individuals. The mechanism of reflex sweating in Case 2 (before operation) was clearly different from that in the other cases. The efferent limb of the reflex arc was furnished by the sympathetic secretory fibres, the response was abolished by sympathectomy and recurred only in a very mild form after degeneration of the sympathetic fibres, when the alternative efferent pathway of accessory fibres was followed. Abnormal sweating phenomena are not infrequent in syringomyelia, of which disease this case was an example, some relation between reflex sweating and the pathological condition in the spinal cord may, therefore, be presumed. The exact cause, however, remains unknown.

Obviously some influence which inhibits reflex sweating in many individuals can be removed by degeneration of sympathetic nerves or by pathological changes in the spinal cord. In this connection the question arises of inhibitory fibres to the sweat glands. Since the experiments of Ott (12) the presence of inhibitory fibres has been frequently suggested, although the available evidence from animal experiment is on the whole unfavourable (9). As regards man, an observation by Foerster (7, 8) indicates that inhibitory fibres may run in the posterior roots. There seems, however, no reason to believe that in our cases reflex sweating was occasioned by interruption of inhibitory fibres in the roots of sensory nerves. In Case 3 reflex sweating did not appear till 2 years after section of the trigeminal root and was clearly related to degeneration of the sympathetic supply.

Can excessive reflex sweating be explained on the hypothesis of destruction of inhibitory fibres in the sympathetic nerves? It might be argued that in Case 2 the pathological process in the spinal cord had involved a tract containing inhibitory fibres to the sweat glands of the face while leaving the secretory fibres intact. The sweat glands would then become, as in fact they were, abnormally reactive to all forms of stimulation. In

Case 3 the appearance of reflex sweating after sympathectomy is compatible with the hypothesis, and a further point in its favour is the distribution of reflex sweating (Fig 3) On the medial side of the right forehead the limit of the reflex sweating area corresponded exactly with the edge of the area of overlap of secretory supply It might reasonably be assumed that inhibitory as well as secretory fibres would be distributed from the opposite side in the area of overlap Moreover it has been demonstrated that adrenaline exerts an inhibitory action, which would be shared by adrenergic sympathetic fibres The hypothesis, however, is not sustained by the results in the remaining cases Division of pre-ganglionic sympathetic fibres, as in the cases of cervico-dorsal sympathectomy, did not lead to reflex sweating, and even degeneration of post-ganglionic fibres was not invariably effective

The phenomenon may perhaps be explained without invoking the assumption of inhibitory fibres to the sweat glands Excessive reflex sweating was invariably associated with a hyperactive condition of the sweat glands as tested by the response to pilocarpine, and conversely when reflex sweating was slight or absent the response to pilocarpine was normal or diminished It seems probable that profuse reflex sweating is related to the hyperactive condition of the sweat glands This abnormally reactive condition of the sweat glands may follow, as in Case 3, degeneration of the sympathetic secretory nerves An excessive response to pilocarpine is a common result of sympathetic degeneration in the cat (1), as in man, however, the effect is not invariable Much more constant is the hyper-sensitive condition of the pupil to adrenaline after sympathetic degeneration (11, 5)

The ultimate cause of the sensitizing effect of denervation has still to be discovered While the excessive degrees of reflex sweating may have been determined by a hyperactive condition of the sweat glands, the slight degrees which followed sympathetic degeneration in the other cases, for example, in Case 4, cannot be so readily explained, because the sweat glands were not in them sensitized to pilocarpine It is possible that some degree of sensitization might have been revealed by a different test

CONCLUSIONS

(1) It has been shown that the sweat glands of the human face have a double nerve supply (a) the sympathetic secretory fibres, and (b) an accessory set of fibres

(2) The sympathetic secretory fibres leave the carotid plexus and join the peripheral branches of the trigeminal nerve, probably extracranially They are distributed with the trigeminal branches and not with the peri-arterial nerves

(3) The accessory secretory fibres arise from the brain stem (probably) and join the trigeminal nerve at some point distal to the sensory root They too, are distributed with the trigeminal branches

(4) The accessory fibres are normally distributed to the sweat glands of the human face. There is, however, no evidence yet available to suggest that they play any important part in sweating reactions under physiological conditions.

(5) The accessory fibres, like the sympathetic secretory fibres, are cholinergic.

(6) Cases of sweating on the face during eating have been described. The sweating was proved to be the result of a reflex. In one case the efferent impulses were conveyed by the sympathetic secretory fibres, in the other cases by the accessory fibres.

(7) The question of inhibitory fibres to the sweat glands has been discussed in relation to reflex sweating during eating.

(8) It is suggested that excessive reflex sweating during eating is related to a hyperactive condition of the sweat glands as indicated by their response to pilocarpine. Such a hyperactive condition may follow degeneration of the sympathetic nerves.

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BASE CHANGES IN THE ALKALOSIS PRODUCED BY THE TREATMENT OF GASTRIC ULCER WITH ALKALIES

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DURING the routine treatment of gastric ulcer with frequent doses of alkalies there occurs occasionally a condition of alkalosis which may produce serious symptoms. Attention appears to have been first called to this complication by Hardt and Rivers (14), and since the publication of their paper numerous cases have been reported from clinics in this country and abroad. A review of the literature dealing with the subject has recently been made by Cooke (6) who has himself studied a number of cases from both clinical and biochemical aspects.

Briefly, the typical clinical manifestations are as follows. The patient, who is taking large doses of alkali for his ulcer, begins to suffer from a feeling of tiredness with impairment of his mental efficiency and powers of concentration. This may be of insidious or of fairly rapid onset. It increases in intensity and soon becomes associated with a definite change of personality, with irritability and unreasonableness, slowness of thought and finally definite drowsiness or even coma.

The mental change is perhaps the most striking manifestation of this type of alkalosis, and its occurrence in any patient who is taking large doses of alkalies should always lead to a suspicion of alkalosis. Sometimes it is of extreme degree, and in one case which came under our notice it actually led to the patient being put under forcible restraint with a provisional diagnosis of general paralysis.

During the period of onset of this mental change some vomiting usually, though not invariably, occurs, but this is not as a rule of the severity encountered in pyloric obstruction. Headaches and generalized muscle pains may be complained of, and conjunctivitis not infrequently develops with sore and red eyes. Although the condition is one of alkalosis, tetany either manifest or latent, appears to be unusual.

The urine is usually increased in amount, frequently exceeding three litres a day. It contains albumen in small but definite amount, and hyaline and finely granular casts are usually present. The concentration of urea

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is low and chlorides are almost completely absent. This low chloride concentration may be a valuable aid in diagnosis. The urine is further usually, but not invariably alkaline, and owing to its high bicarbonate content effervesces on addition of acid.

The changes encountered in the blood have been summarized by Cooke (6). They may conveniently be divided into two groups. First are those typical of an uncompensated alkalosis, namely, raised pH, high plasma bicarbonate and low plasma chloride, the rise in the former approximately balancing the fall in the latter. Secondly there is a group of changes referable to a seriously impaired renal function. These include high blood urea and non-protein nitrogen, high plasma creatinine and raised plasma phosphate. The finding of a raised blood urea is an extremely valuable point in diagnosis and when present in a patient with gastric ulcer who is showing suspicious symptoms and who has no history or evidence of previous renal disease it is practically diagnostic.

On stopping the administration of alkalis the condition of alkalosis is rapidly cured. Careful treatment with acidifying drugs such as ammonium chloride hastens the process. The plasma bicarbonate returns to normal in a few days, normal mentality is speedily restored and the conjunctivitis clears up. But the signs of renal damage are more persistent, albuminuria tending to continue for a week or two, and the blood urea not returning to normal figures perhaps for several weeks.

This interesting condition appears to result directly from the excessive administration of alkalis. The dosage of alkalis commonly employed in the treatment of gastric ulcer produces alkalosis in only a relatively small group of patients. In some individuals it may be produced by only a few days on an alkaline regime which in the great majority of ulcer patients causes no ill effects. Or it may develop relatively rapidly in a patient who has been taking alkalis for long periods of time without apparent harm. The cause of this unusual sensitivity to alkalis is at present undetermined.

It is certainly not usually referable to a previously impaired renal function. On recovery from the attack the albuminuria clears up completely and renal function returns to normal. In the most sensitive patient encountered in this work, a man who had had four severe attacks of this alkalosis, the renal function estimated by the urea clearance method after recovery from the fourth attack was 92% of normal.

The condition has now been studied by a number of observers and the characteristic changes in the acidic radicles in the blood are well established. But possible changes in the basic radicles do not as yet appear to have attracted the attention of investigators. This is particularly surprising when it is realized that anions are on the whole pharmacologically more active than cations and that the treatment which initiates these symptoms involves the ingestion of excessive quantities of anions. Some of the changes in the concentration of various anions in the blood have, therefore, been followed in several examples of this form of alkalosis.

In discussing the findings this type of alkalosis will, for convenience, be referred to as alkali alkalosis to distinguish it from other types of alkalosis such as that resulting from the vomiting associated with pyloric obstruction, a type from which it differs in several respects

Methods

Serum total base was determined by the method of Stadie and Ross (22) In normal subjects this method has given in our hands consistent results within accepted normal limits

For the estimation of serum calcium the method of Halverson and Bergeim (13) was used in order that the filtrates might subsequently be available for serum magnesium determination All estimations were done in duplicate and were in good agreement with one another

Estimations of serum magnesium were made by the method of Briggs (3) on the filtrates from the Halverson and Bergeim calcium estimation The phosphate in the ammonium-magnesium phosphate precipitate was determined by the stannous chloride method of Youngburg and Youngburg (24) in the majority of the estimations, this being found definitely more satisfactory than the method of Fiske and Subbarow (11) using aminonaphtholsulphonic acid which we employed in some of the early estimations By both methods duplicate determinations which were always carried out, were in good agreement, usually within 5%

The total base content of the serum

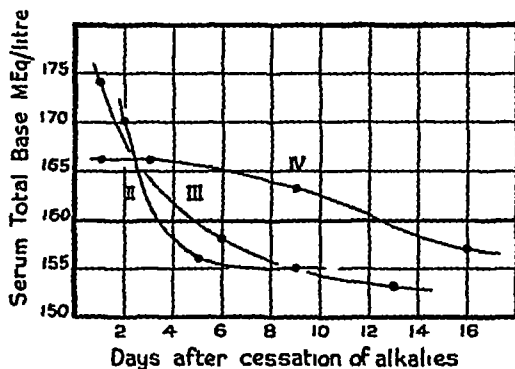
Under normal and the great majority of pathological conditions the body maintains the total base content of the serum with considerable tenacity within very narrow limits The extremes of normal variation are generally accepted to be only between 150 and 160 mEq per litre Variations beyond these limits are encountered in very few conditions, but prominent among these is prolonged vomiting such as results from pyloric obstruction, and in this state it may be greatly reduced, even to below 130 mEq per litre

The clinical picture presented by alkali alkalosis shows many points of similarity with that of severe pyloric obstruction In both there is a marked uncompensated alkalosis associated with considerable disturbance of renal function and with nitrogen retention It was of interest, therefore, to study the total base changes in the serum in the former condition The changes in serum total base occurring during recovery from alkali alkalosis have been followed in three cases The results are shown graphically in Fig 1 In all three cases the serum total base is at first slightly but significantly raised above the normal upper limit, and in all three it returns to normal during the recovery period

This raised total base is in marked contrast to the findings in the alkaloses of pyloric obstruction and other forms of severe vomiting, for in these a considerable reduction in its concentration is characteristically encountered This contrast is reflected in the clinical picture The work

of Gamble and others has shown that loss of base from the body is usually associated with dehydration. Such dehydration is well marked in pyloric obstruction in which it is revealed by the dry tongue, the sunken facies, the concentrated blood and the scanty concentrated urine. But in alkali alkalosis such signs of dehydration are commonly completely absent. Instead of oliguria there is more usually a polyuria and there is no trace of the sunken look typical of dehydration. It seems justifiable to attribute this clinical difference to the difference in the body content of total base in the two conditions, this being reflected in the concentration in the serum.

Figure I
Serum Base in Gastric Alkalosis



The actual cause for this difference is not far to seek. In pyloric obstruction large quantities of base are lost in the vomit and are not replaced. In alkali alkalosis on the other hand the vomiting is less severe and quantities of base are continually being ingested and absorbed and are more than adequate to replace any loss. For this reason serum total base tends to be above rather than below normal in this condition and so dehydration does not readily occur.

It is possible further, that the polyuria present in these patients is due at least in part to the excessive base excretion. Recent work by Gamble, McKhann, Butler and Tuthill (12) has shown that in rats an increased excretion of inorganic salts (such as follows increased intake) results in an increase in the daily output of urine. In our alkalotics large quantities of such salts were being excreted in the urine. We have noticed a tendency for the total base concentration of the urine to approximate to that of the blood, any increase in base excretion being brought about mainly by an increase in the volume of urine with but little change in the urine base concentration. Judging from the work of Davies, Haldane and Peskett (8) who found that the sum of the concentrations of bicarbonate and chloride in the urine could not be raised above 330 mEq per litre, this apparently optimum base concentration—150 mEq per litre—would be about half the

maximum obtainable. The suggestion has sometimes been made that the urea retention occurring in alkalotics is a compensatory phenomenon designed to restore to normal the osmotic pressure of the blood crystalloids which have been reduced as a result of the excessive loss of sodium chloride. In view of the fact that urea appears to diffuse equally through all the body fluids this suggestion has always seemed improbable, and the present series of cases greatly strengthens this doubt in that an alkalotic uræmia is present in the absence of any diminution in the concentration of blood crystalloids.

Nor clearly, are oliguria and dehydration essential factors in the production of alkalotic uræmia for in the present type of case these also are absent.

Serum calcium

The alkaline powder taken by our gastric ulcer patients who developed alkalosis contained a considerable quantity of calcium carbonate, the approximate daily intake from this source being 7 grams. It appeared of interest, therefore, to follow the serum calcium in such cases. A control series of eleven subjects who had been undergoing the same alkaline regime without developing any symptoms or signs of alkalosis gave values well within normal limits (Table I). The highest figure was 10.5 mg, the lowest

TABLE I

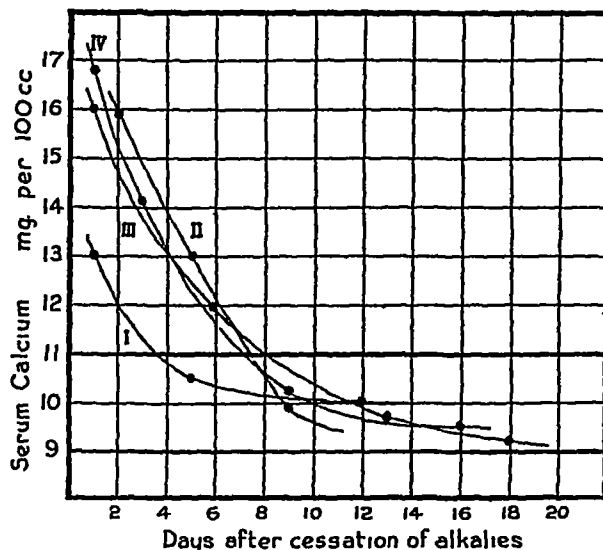
Serum calcium and magnesium in gastric ulcer patients undergoing routine alkali treatment

Case No	(mg per 100 c c)		Case No	(mg per 100 c c)	
	Serum Ca	Serum Mg		Serum Ca	Serum Mg
1	9.7	1.95	7	9.1	1.93
2	10.0	1.95	8	10.5	2.17
3	9.5	2.26	9	9.6	2.63
4	9.7	2.07	10	9.3	2.13
5	10.4	1.82	11	10.2	1.89
6	9.9	1.85			

9.1 mg and the mean 9.8 mg per 100 c c. There is thus no evidence that the continued ingestion of the quantities of calcium carbonate contained in this powder causes any appreciable rise in the blood calcium level in individuals who are not alkali sensitive. But in all the four cases of alkalosis which we have examined a raised serum calcium has been found which has returned slowly to normal during the period of clinical recovery. The rise is often of considerable degree. In three of the cases serum calcium of 10 mg or over were observed. And in view of the rapidity of the fall to

normal after cessation of alkali administration it is safe to assume that even higher concentrations—probably 18 mg or more—were prevailing at the time that alkalis were withdrawn (Fig 2)

Figure II
Serum Calcium in Gastric Alkalosis



So far as we are aware it is not generally recognised that such a degree of hypercalcaemia can be produced by ingestion of calcium salts. That calcium ingestion is the actual cause seems fairly certain. Hypercalcaemia is not usually present in the alkalosis caused by pyloric stenosis. Tisdall (23) for instance, in two cases of tetany caused by severe vomiting found serum calcium of 10.0 and 10.6 mg. And we have been able to observe one case in which a typical alkalosis was produced by a combination of severe vomiting and excessive potassium citrate ingestion the patient being under treatment for pyelitis. In this case no abnormal quantity of calcium had been ingested and the serum calcium was normal, 10.0 mg per 100 c.c. (Case 6). It must be admitted that Hastings, Murray and Murray (15) noted moderate rises in serum calcium in their dogs with experimental pyloric obstruction but this may well have been due to the concentration of the blood produced by the severe loss of fluid in the vomit.

But excessive calcium ingestion alone is clearly not the sole cause of the hypercalcaemia, for in normal individuals it is not easy to raise the concentration of serum calcium far above normal by giving calcium salts by mouth (21), and our control series of similarly treated cases which remained free from symptoms showed no tendency to develop hypercalcaemia. It seems probable, therefore, that the renal impairment first occurs and that this

renders the kidney unable to excrete sufficiently rapidly all the calcium which continues to be absorbed from the gut. Our knowledge of the effect of renal damage on the ability of the kidney to excrete calcium is still very scanty, but Hetényi and von Nográdi (17) have found that intravenously injected calcium is excreted more slowly by nephritics than by normal persons. We have attempted without success to follow the stages of development of the alkalosis, but the renal damage and biochemical changes are usually well established when clinical evidence of the condition is first recognizable. We tried in one case deliberately to provoke the onset of alkalosis in a man who was well known to be alkali sensitive, but he asked that the experiment should be discontinued at a time when no change had occurred in the blood chemistry or in the renal function. His reason was that he felt the onset of typical early mental symptoms, but these were probably imaginary as he was fully aware of the nature of the experiment. Further, we have submitted a known nephritic suffering from mild nitrogen retention to the routine alkaline regime used for gastric ulcer treatment but only a slight rise in serum calcium took place in a week, and renal function as judged by the urea clearance remained absolutely unchanged. We have thus been unable to ascertain definitely the cause for the calcium retention in these cases.

We have already noted that tetany seems to occur relatively infrequently in this type of alkalosis. It was present in none of the five cases which we studied, and was reported in only one of the nine cases published by Cooke (6). It seems possible that the hypercalcaemia occurring in these patients is a factor tending to reduce the incidence of tetany. Although the pathogenesis of the tetany associated with alkaloses is not well understood and its relation to serum calcium is obscure, yet it seems not unreasonable to suppose that a rise in the serum calcium and so in the concentration of ionized and physiologically active calcium may tend to counteract the tendency to tetany caused by the alkalosis itself. But such a suggestion must clearly be made with reserve because calcium administration or the raising of the serum calcium has apparently not been shown to be of definite therapeutic value in cases of tetany of alkalotic origin unassociated with obvious disorder of calcium metabolism.

Usually when serum calcium rises there is an approximately proportional fall in the phosphate, the product of the two tending not to exceed 40 to 50. This reciprocal relation is not infrequently very clearly demonstrable in cases of tetany due to hypocalcaemia in which the serum calcium is made to vary under the influence of parathormone or calciferol administration. But in alkali alkalosis this reciprocal relation is not observed and the high serum calcium tends to be associated with a rise rather than with the more usual fall in the phosphate concentration. Hence the calcium phosphorus product may greatly exceed the normal limits. In those of our cases in which plasma phosphate determinations were done the plasma phosphate was always slightly or definitely raised. In all the cases reported by Cooke also (6) it was above normal and in some at least of his cases we may safely

assume that the serum calcium was raised. In our most marked case a serum calcium of 15.9 mg was associated with a phosphate in the plasma of 6.85 mg the product of the two thus being 109. The existence of such a product indicates that at least under some conditions serum is capable of holding in solution considerably higher concentrations of calcium phosphate than those normally present. The solvent power of the serum for calcium phosphate is known to be greatly influenced by the protein concentration of the serum and empirical equations have been developed correlating the three variables calcium, phosphorus and protein. It is, therefore, unfortunate that plasma protein estimations were not performed in our cases of gastric alkalosis. But it is possible to deduce from the equation of Peters and Eiserson, which was evolved from a study of human clinical material, that a calcium phosphorus product of 109 would require a protein concentration of some 19 grams per 100 c c, a figure which is highly unlikely to have been present.

Comparable high calcium phosphorus products are encountered so far as we are aware, in only one other condition, that brought about by parathormone overdosage or by parathyroid hyperactivity. If parathormone is injected at three or four hour intervals into a dog, the rise in serum calcium is at first associated with a fall in phosphate. If, however, the injections are continued, serious toxic symptoms develop and, with the onset of these, the plasma phosphate rises to values much above normal with but little reciprocal fall in the calcium. In one such experiment reported by Collip (4) a calcium phosphorus product of over 250 was finally reached in a dog. A similar phenomenon may apparently rarely be encountered in man. Bellin and Gershwil (2) have recently reported a case of hyperparathyroidism with renal insufficiency in which the calcium phosphorus product was 133. And Albright (1) in the previous year had noted that when hyperparathyroidism leads to renal damage from calcium precipitation in the renal tubules then the associated hypophosphatemia disappears.

Now parathormone overdosage and alkali alkalosis have in common not only this high calcium phosphorus product but also considerable renal functional damage manifested by serious nitrogen retention. In neither condition is the cause of this renal damage clear. But Collip (5) has shown that in dogs a high calcium phosphorus product is itself toxic to the kidneys, for the simultaneous intravenous injection of calcium salts and of sodium phosphate has been shown by him to cause severe renal functional damage and nitrogen retention. The fact that a high calcium phosphorus product in the serum is apparently only encountered clinically in the presence of renal damage would appear, therefore, to be of significance. But whether renal inadequacy renders possible the existence of such a high product, or whether the high product produced by independent causes is itself the actual cause of the renal damage cannot be definitely decided on the evidence at present available. We feel, however, that the second possibility is unlikely for in Case 6 previously referred to, renal inadequacy developed in the absence

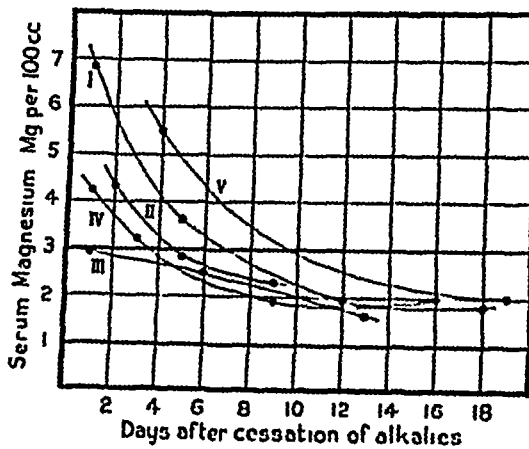
of any significant change in the calcium-phosphorus product. It was, of course, possible that the pyelitis present was in this case responsible for the renal damage, but the clinical impression gained at the time was that this was a quite inadequate cause.

Serum magnesium

It is usually stated that the concentration of magnesium in the blood serum is practically uninfluenced by any pathological condition (21), and Hawk and Bergeim (16) dismisses its clinical significance with the remark that "no characteristic changes have been observed in pathological conditions" (page 463). The alkaline powder taken by our gastric patients who developed alkalosis contained considerable quantities of magnesium, but it was nevertheless not this fact which first aroused our interest in the behaviour of the serum magnesium in this condition. It had been shown by Cramer (7)

Figure III

Serum Magnesium in Gastric Alkalosis



that prolonged magnesium lack in rats may cause serious renal damage, and it is also known that when the contents of the alimentary canal are kept alkaline the absorption of calcium and of magnesium is impaired. It was these considerations which led us originally to suspect that the renal damage in these alkalotics might be associated with an actual magnesium deficiency and that this might be shown by a reduction in the serum magnesium. Investigation of this hypothesis however, showed that actually the reverse is the case. The serum magnesium was in all cases raised, and in some considerably so. In a control series of eleven cases who had been on the ulcer regime with alkaline powder for several weeks, and who had remained free from any evidence of alkalosis, the serum magnesium was always well within the generally accepted normal limits of 1 to 3 mg per 100 cc. The highest figure was 2.03 mg and the remaining ten fell between 1.82 and 2.26 mg the mean of all eleven being 2.06 mg (Table I).

The magnesium concentrations in the five cases of alkali alkalosis which we have studied were all above the highest value in the control group. In four of the five the serum magnesium shortly after the cessation of alkali administration was above 4 mg per 100 c.c. The highest actually observed figure was 6.84 mg. In all cases the magnesium returned to normal within a fortnight (Fig. 3).

Such a rise in the serum magnesium is not a usual accompaniment of severe nitrogen retention in ordinary uræmia of nephritic origin. Denis and Hobson (9) for instance, have reported the serum magnesium to be unaltered in renal insufficiency. We have ourselves determined the serum magnesium in four advanced nephritics and obtained the following values (Table II).

TABLE II
Urea, calcium and magnesium in nephritic cases

Case	Blood urea mg per 100 c.c.	Serum Calcium mg per 100 c.c.	Serum magnesium mg per 100 c.c.
1	550	9.6	2.83
2	220	6.2	3.25
3	150	10.2	2.5
4	120	—	2.54

The serum magnesium thus does not run parallel to the blood urea, and although the figures are above those obtained in our control group of gastric ulcer cases, they scarcely exceed the upper limit of normal accepted by most workers, 3.0 mg. Nor does nitrogen retention of alkalotic origin appear to be necessarily associated with a rise in the serum magnesium for in the case previously referred to in which alkalosis developed as a result of vomiting and much potassium citrate administration, the serum magnesium was only 2.55 mg at a time when the blood urea was 318 mg.

But it would be untrue to claim that alkali alkalosis is the first clinical condition in which high blood magnesium concentration has been encountered in man, for Hirschfelder (18) has recently called attention to the fact that even higher values may be found in nephritics to whom magnesium sulphate has been administered as a purgative. In such cases it would appear that absorption of magnesium from the gut is more rapid than excretion by the damaged kidney, and figures as high as 11 mg per 100 c.c. have been found by him. In view of Hirschfelder's findings it seems highly probable that the hypermagnesiæmia of our alkalotics is also due to the continued administration of magnesium salts after the kidney has become damaged and unable sufficiently rapidly to excrete them. The fact that no hypermagnesiæmia developed in the above-mentioned case which became alkalotic as a result of potassium citrate therapy for pyelitis also supports this view.

It would seem that magnesium is very largely excreted by the kidney in normal circumstances, and during the recovery period when the serum

magnesium is returning to normal in these alkalotics abnormal quantities of magnesium are excreted in the urine. In one of our cases (Case 1) the daily excretion of magnesium in the urine was followed throughout the recovery period. During the period of observation the diet was kept approximately constant. During the first few days, when the serum magnesium was high the daily excretion of magnesium in the urine was about 300 mg per day. As serum magnesium fell so did the urinary excretion diminish until both in ten days reached a basic steady level of 50 mg per day. The total magnesium excreted in the urine in excess of this basal level, and so the minimum amount of magnesium retained abnormally in the body was approximately one gram. Unfortunately we were unable to follow the excretion of magnesium in the stools in this case, so that the total amount of retained magnesium may have been even greater.

In relation to the symptomatology of the alkalosis this hypermagnesaemia is of possible interest from two points of view. In the first place magnesium is now well known to exert a strong depressant action on nervous and muscular tissues. It was this property which was made use of by Meltzer and Auer (19) in the method of treatment which they suggested for the muscular spasms of tetanus. And Emmanuele (10) for the same reason has used it with success in the treatment of infantile tetany. Presumably, therefore, the hypermagnesaemia in this type of alkalosis is an additional factor counteracting any tendency to tetany caused by the actual alkalosis. In the second place the hypermagnesaemia may well account for some at least of the peculiar mental symptoms of the condition. Hirschfelder (18) has shown that when the serum magnesium rises above 8 mg per 100 c.c. in man drowsiness is liable to occur. And Neuwirth and Wallace (20) have shown that in dogs and in man a serum magnesium of 5 to 6 mg exerts a mild sedative action. The serum magnesium values which we have observed after the cessation of alkali administration have approached these pharmacologically active levels and were presumably even higher whilst alkalis were still being taken. They were furthermore probably acting for a longer period of time than in the experiments of Hirschfelder and of Neuwirth and Wallace and in view of these facts it seems reasonable to suppose that the retained magnesium did exert some sedative action on the cerebral functions, and that it may indeed have been responsible in part for the mental symptoms.

General discussion

It is already known that in this type of alkalosis which develops during the alkaline treatment of gastric ulcers, renal functional impairment is marked and results in a severe degree of nitrogenous retention, and in an abnormal accumulation of the bicarbonate ion in the blood. In the present paper it is shown that the inorganic basic radioles in the alkaline powder, especially calcium and magnesium, also tend to accumulate. It is suggested that this accumulation may well be responsible in part for some of the characteristic symptoms of the condition.

It cannot be claimed that the demonstration of this accumulation throws any certain light on the ætiology of the renal damage itself. The probability is that it is the direct result of this damage. The evidence so far available suggests that the damaged kidney is unable to excrete the inorganic substances concerned as fast as they are absorbed from the alkaline powder. As soon as the excessive intake is stopped the kidney is able to restore rapidly the normal blood concentrations of calcium, magnesium and bicarbonate. But the rapid return of these to normal levels cannot be taken as evidence of a fully restored renal function, for albuminuria and high blood urea persist for a considerably longer time. The renal damage only recovers completely after two to four weeks. But the typical symptoms which are associated with alkali alkalosis have usually disappeared by the time the inorganic constituents of the blood have returned to normal. They do not persist as long as the nitrogen retention, and, since the clinical picture differs markedly from that known to result from such retention, there is no justification for believing it to be the cause of the symptoms.

The peculiar symptoms have been shown to be associated with unusual changes in the concentrations of certain inorganic constituents of the blood, changes which are rarely, if ever, encountered together in other disease states. It is tempting to suggest, therefore, that retention of these inorganic substances is concerned in the ætiology of the typical symptoms, for their development is clearly related to the ingestion of simple alkaline inorganic compounds. But of the precise role which bicarbonate excess, chloride lack, hypercalcaemia and hypermagnesaemia play in the production of the clinical picture it is scarcely possible definitely to judge at the present time.

SUMMARY

- 1 Several cases of alkalosis developing as a result of the alkali treatment of gastric ulcer have been studied, and the changes occurring in certain of the inorganic basic constituents of the blood have been followed.
- 2 The serum total base has been found to be slightly but significantly raised.
- 3 The serum calcium is raised very considerably above normal limits.
- 4 The serum magnesium is also definitely above normal.
- 5 The bearing of these changes on the ætiology of the symptoms is considered.

CLINICAL NOTES

Case 1 A man, aged 51, who visited his doctor on July the 4th on account of slight indigestion. Two days later he had an attack of vomiting with hæmatemeses, diarrhoea and melæna leading to collapse. He was given a gastric diet with alkalis* and improved for three or four days, but then had another attack of vomiting with partial collapse. He rapidly developed headaches, sore eyes and severe general mental disability leading to a semi comatose condition in which he was admitted on July the 22nd.

On admission he was restless and in light coma. The tongue was furred and there was definite conjunctivitis but no other abnormal signs. The urine was alkaline, contained only a trace of chloride, many hyaline casts and a good cloud of albumen. He was treated for two days with rectal salines with 5% glucose. On July the 25th ammonium chloride 8 g was added to the rectal saline six hourly. On July the 26th the mental condition was much improved, but he was still dazed and emotional and did not remember the events of the previous week. July

* The approximate daily intake of alkali from this source was sodium bicarbonate 7 g, magnesium carbonate 70 g, calcium carbonate 7 g and bismuth oxy carbonate 180 g.

the 27th, the saline was discontinued, albumen and casts were still present in the urine. His general condition steadily improved on a light gastric diet without added alkalis, and was quite normal by August the 8th when the urine became albumen free.

	July 23	July 27	Aug 3	Aug 9
Blood urea (mg per 100 c c)	225	211	85	74
Plasma bicarbonate (vols %)	105	50	68	—
Plasma chloride (mg per 100 c c as NaCl)	—	658	572	594
Plasma inorganic phosphate (mg per 100 c c)	4.4	4.5	—	—
Serum calcium (mg per 100 c c)	13.0	10.5	10.0	9.2
Serum magnesium (mg per 100 c c)	6.84	3.6	1.94	1.82

Case 2 A woman, aged 50, with a seven years' history of epigastric pain 1 to 2 hours after meals, with occasional vomiting. No evidence of gastric or duodenal ulcer was revealed by X ray. She had been taking alkalis for the last three years. Pain had become much worse five weeks before admission and melena being found, she was admitted on February the 12th. Apart from epigastric tenderness there were no physical signs. On February the 14th the stools no longer contained occult blood. She was put on routine gastric ulcer diet with alkalis*. On February the 19th she complained of nausea before meals and vomited occasionally but became free from pain. On March the 9th, she became mentally abnormal, with drowsiness and irritability and was found to have marked conjunctivitis. The urine was alkaline and gave a cloud of albumen. The blood urea was 210 mg %. Alkalis were at once stopped, and without further treatment than this her mental condition was fully restored to normal by March the 20th, although slight conjunctivitis was still present. The urine became acid on March the 21st and ceased to contain albumen on March the 26th at which time the blood urea was still 97 mg %.

	March 11	March 14	March 18
Blood urea (mg per 100 c c)	275	247	204
Plasma bicarbonate (vols %)	92	75	63
Plasma chloride (mg per 100 c c as NaCl)	498	533	551
Plasma inorganic phosphate (mg P per 100 c c)	6.85	7.2	6.95
Serum calcium (mg per 100 c c)	15.9	13.0	9.9
Serum magnesium (mg per 100 c c)	4.33	2.80	2.29
Serum total base (mEq per litre)	170	156	155

Case 3 A man, aged 55, with fifteen years' history of intermittent epigastric pain and tenderness, which has recently become more severe. He suffered from frequent vomiting after meals. His pain was much relieved by alkalis, of which he had been taking considerable amounts before admission on February the 1st. No physical signs found except an emphysematous chest. Occult blood was present in the stools. He was put on routine gastric ulcer diet with alkalis*. One week later he complained of a throbbing in the head and was sleepless and restless. On February the 9th he had severe headache, anorexia, smarting eyes and definite drowsiness. There was conjunctivitis and the urine contained albumen. The blood urea was 112 mg %. Alkalis were stopped and his condition rapidly returned to normal. His mean daily urine output for the week during which alkalis were given was 76 ounces and his mean daily urine output for twelve days following withdrawal of alkalis 50 ounces.

	Feb 9	Feb 14	Feb 21
Blood urea (mg per 100 c c)	112	108	60
Plasma bicarbonate (vols %)	101	68	64
Plasma chloride (mg per 100 c c as NaCl)	533	595	622
Plasma inorganic phosphate (mg P per 100 c c)	—	—	2.7
Serum calcium (mg per 100 c c)	16.0	12.0	9.7
Serum magnesium (mg per 100 c c)	2.9	2.56	1.59
Serum total base (mEq per litre)	174	158	153

Case 4 A man, aged 57, admitted to hospital on June the 3rd. There was a fifteen years' history of gastric trouble for which he had been taking alkalis at times. Five years previous to admission he had been operated on for gastric ulcer (? gastro-enterostomy). He had been taking about four drachms of alkali daily ever since, but had still further increased the amount during the last six months as the pain had recurred. During the last few months he had become progressively weaker, had lost his previously good appetite, had become irritable and depressed and had himself noticed diminishing mental efficiency. A fortnight before admission he went for a holiday on the advice of his doctor who considered him to be suffering from a "nervous breakdown". During this fortnight he continued to take his alkalis and the holiday did him no good. He vomited five times during that time. On his return he came straight to hospital and was found to have albuminuria and conjunctivitis, and to be definitely drowsy. He was admitted at once as a typical case of alkalosis. His blood urea was then 201 mg %. No treatment other than the complete withholding of all alkalis was employed and he made an uneventful recovery, the urine becoming free from albumen on June the 11th.

	June 4	June 6	June 12	June 19
Blood urea (mg per 100 c c)	201	208	82	57
Plasma bicarbonate (vols. %)	101	91	63	57
Plasma chloride (mg per 100 c c as NaCl)	471	572	620	632
Plasma inorganic phosphate (mg P per 100 c c)	4.3	4.2	2.75	—
Serum calcium (mg per 100 c c)	16.8	14.1	10.2	9.5
Serum magnesium (mg per 100 c c)	4.18	3.17	1.88	1.96
Serum total base (mEq per litre)	166	166	163	157

Case 5 This case, although less completely investigated, is included because of the marked magnesium retention which it showed. A man, aged 46, admitted to hospital on December the 20th with a diagnosis of pyloric obstruction. He had been taking alkalis for years previously and had never had any drowsiness. He was treated by stomach washouts with sodium bicarbonate solution, and with alkaline powder by mouth, 4 g three times a day. On January the 4th he became markedly drowsy and developed slight soreness of the eyes. Albuminuria was present and the blood urea was 261 mg %. All alkali administration was at once stopped but severe vomiting occurred throughout the following week. On January the 8th serum magnesium was 5.5 mg, blood urea 237 mg. By January the 10th blood urea had fallen to 142 mg. On January the 24th, blood urea was 43 mg, serum magnesium 2.0 mg, and serum total base 160 mEq per litre. He was by then entirely free from alkalotic symptoms.

Case 6 A case in which alkalotic symptoms developed as a result of potassium citrate medication. Reported for comparison of its biochemical picture with that of the cases of gastric alkalosis. The patient was a married woman of 21, admitted on March the 5th with pyelitis. She was 5 months' pregnant. Her urine was acid and contained albumen and numerous pus cells, but no casts. The blood pressure was 110/70. Potassium citrate was administered in increasing doses but the urine only occasionally became slightly alkaline. By March the 15th she was receiving 4 g of potassium citrate every three hours, and continued to do so until March the 30th. During the last ten days of this treatment she vomited several times, and finally became irritable and unreasonable, and developed a mild conjunctivitis on March the 30th. On April the 1st the blood urea was 273 mg, the urine was acid and contained a trace of albumen. There was no oedema and the blood pressure was normal. Citrate administration was stopped and on April the 3rd the blood showed the following figures:—Blood urea 318 mg, plasma bicarbonate 75 vols, plasma sodium chloride 433 mg, serum calcium 10.0 mg, serum magnesium 2.55 mg, plasma inorganic phosphate 4.44 mg per 100 c c, serum total base 139 mEq per litre. No further citrate was given and the patient steadily recovered. By April the 25th the blood urea was only 20 mg per 100 c c, and the urine was albumen free.

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VASODILATATION AND VASOCONSTRICTION IN RESPONSE TO
WARMING AND COOLING THE BODY A CRITICISM
OF METHODS *

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IN recent years increasing attention has been paid in patients suffering from nervous maladies to those symptoms and signs which suggest disturbance of the sympathetic nervous system. Analysis of these symptoms and signs depends upon accurate observation of environmental conditions and of effects produced by changing the conditions. It was decided to make on normal subjects a series of observations, especially of skin temperature, as indicating states of vasodilatation and vasoconstriction. The purpose of this paper is to record these investigations, the methods adopted, the difficulties encountered and to discuss the results.

Method

Temperature readings of the skin were made by means of constantan and copper thermojunctions in contact with the tips of the fingers, the tips of the toes and the cheeks. Readings were also obtained from the skin surface of other regions of the body. Rectal temperature was recorded by means of a thermojunction placed 5 to 6 cm within the anal sphincter. The rectal thermojunction was of a particular type, designed to give rapid registration of temperature change. A hollow finger-like copper structure of low thermal capacity fixed to a vulcanite end grooved to permit the sphincter ani to close upon it, constituted the heat receptor from the rectal mucosa. Into the thin piece of copper were soldered two wires, one constantan and the other copper. In the rectal thermojunction a difference of potential proportional to the temperature of the copper was measured against a constant difference of potential in a second thermojunction kept at a constant temperature of 37°C. The difference between the currents in the two thermojunctions was registered on a high sensitivity mirror.

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galvanometer By means of a factor determined by physical experiment and found to be constant over temperature variations such as were recorded, the amount of deflection above or below a zero mark was translated into terms of temperature in degrees centigrade and subtracted or added to 37°C Thus the rectal temperature was obtained at any point of time The limitations of this method are a necessary lag on the part of the rectal thermojunction in virtue of thermal capacity, and a small lag, of maximum twenty-two seconds, in the galvanometer itself Although no claim is made that the rectal temperatures recorded here are absolute, it is certain that changes of temperature are registered with reasonable rapidity

Two methods of producing vasodilatation were adopted In one, the subject lay on his back, the trunk was enclosed in a blanket box so that the head, hands and feet protruded, a series of carbon filament lamps, suspended from the top of the box, provided a source of heat The direct effect of radiant heat on the skin of the trunk was minimized by shielding the lamps with a sheet of asbestos The sheet of asbestos was adjusted so that a free circulation of air ensured the warming of the whole box In the other method, the subject either sat or lay on a couch two limbs from which observations were not being taken, were placed and kept gently moving in tanks of water at 44°C to 45°C This method is similar to that described by Gibbon and Landis (1) After adequate warming had occurred, the limbs were transferred to tanks containing water at 9°C to 12°C When adequate cooling had been registered the limbs were again immersed in water at 44°C to 45°C By this method repeated warming and cooling could be effected in one subject in the course of two hours

The room in which the subjects sat or lay was rendered as nearly draught-free as possible It was possible to raise the temperature of the room at will In this way varying external conditions were available

Experimental material Over two hundred experiments have been carried out These have dealt with the vasomotor response to warming and cooling the body For the purpose of clarity only a few representative experiments will be described A series of experiments was carried out on four subjects, three of whom were healthy young adults with no recognizable disease of the blood vessels or nervous system, the fourth suffered from orbital neuralgia Both methods of warming were employed in studying two subjects, several experiments using each method of heating were carried out in both of these subjects In the other two subjects only one method of heating was utilized Experiments on two patients with a fractured spine will also be quoted

Results

It is difficult to tabulate clearly the results of these experiments, therefore the interpretation of isolated experiments illustrative of each group will be discussed Having considered each experiment in this manner a final review will be made from which conclusions will be drawn It is

assumed that a rise in skin temperature indicates dilatation of blood vessels and a fall in temperature constriction

Experiment 1 Fig 1 A, 25/11/33, a young healthy male, lay on a couch covered with blankets, the face only being exposed. Temperatures were recorded from the rectum, from the tips of both third fingers and great toes. The room temperature rose from 14°C to 20°C during the five hours of the experiment

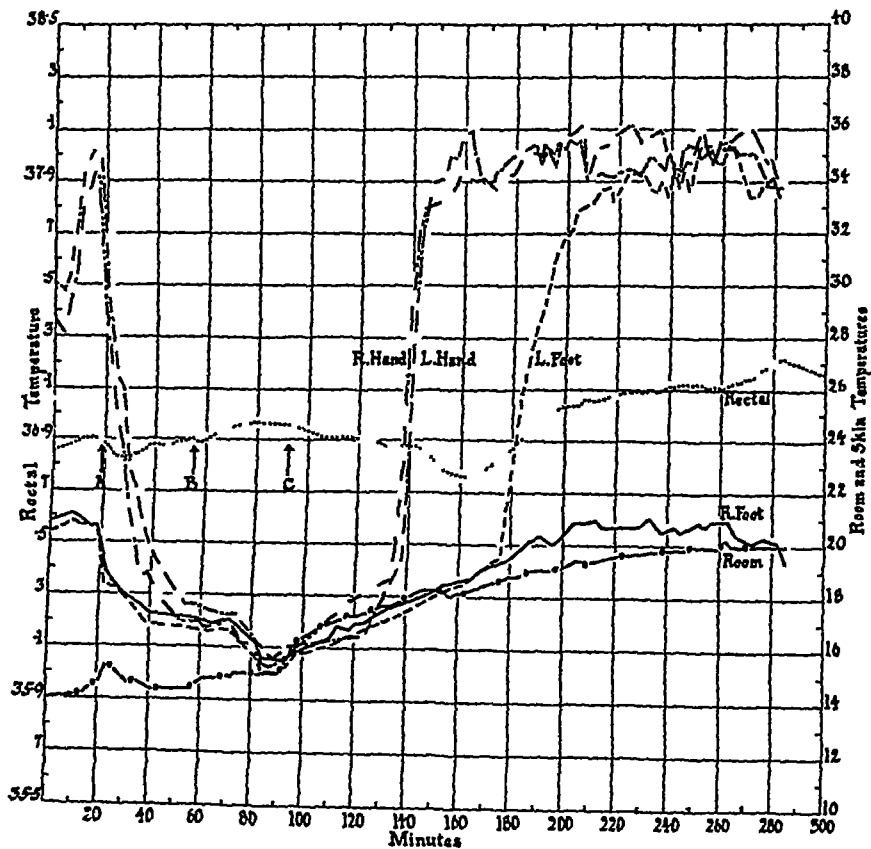


Fig 1

For the first seventeen minutes, while the subject lay covered with blankets, the rectal temperature rose slowly, 0.05°C , the temperature of the fingers rose 5.0°C , but that of the toes remained stationary. At A, 19 minutes after the commencement of the experiment, the hands and feet were uncovered. Immediately the temperature of all four digits fell, and at the end of the 53rd minute the readings were approximately equal in the region of 17.0°C . Following the exposure of the hands and feet, the rectal temperature commenced to fall, continuing to do so for 9 minutes, it

reached 36.82°C , a fall of 0.07°C , thereafter it commenced to rise slowly during a period of 26 minutes, at the expiry of which time the blankets were completely removed at B, the 55th minute. After the removal of the blankets from the body the rectal temperature fell 0.01°C in $2\frac{1}{2}$ minutes, and then commenced slowly to rise. At C, the 92nd minute, the subject was covered with the hot air bath leaving the head, hands and feet exposed. The heat was turned on and the temperature of the fingers and toes slowly rose till the 136th minute, the fingers from 15°C to 18.5°C , and the toes from 15°C to 17.5°C , which increase in temperature corresponded to the rise in room temperature. The temperature of the fingers then rapidly increased to 34°C . From the time of turning on the heat the rectal temperature fell very slowly, immediately after the rise in temperature of the fingers it fell more rapidly, 0.12°C in 20 minutes. The rectal temperature then began slowly to rise and at the 176th minute of the experiment, 84 minutes after applying the heat, the temperature of the left great toe commenced to rise. Following this the rectal temperature rose more rapidly, nevertheless, at the end of the experiment, 110 minutes later, it had only risen 0.45°C . The main rise took place within 25 minutes of the rise in temperature of the left toe. Even at the end of the experiment the temperature of the right toe did no more than follow the room temperature.

Several observations were thus made. First, was the insignificant effect of the hot air bath upon the rectal temperature. Although the air within the hot air bath rose to a temperature of over 50°C no marked rise in rectal temperature occurred. This observation suggests that the method of heating employed was inadequate to effect a rise in rectal temperature. Secondly, the alteration of rectal temperature associated with the various manipulations claims attention. Following the exposure of the hands in a warm state, and the feet in a cold state, to the cool air of the room, a fall in rectal temperature occurred. Again when the blankets were removed from the trunk a further fall in rectal temperature was registered, this fall was of slightly less degree than that following exposure of the warm hands to the cool atmosphere. Yet again, when the hands warmed following the turning on of the heat, the rectal temperature fell. These observations point to the extreme delicacy of control over rectal temperature which may be played by the state of the blood vessels of the skin. Thirdly, it is of importance to note that the vessels of the toe of only one foot dilated although the experiment lasted three hours after applying the heat.

It becomes, therefore, a necessity to attempt to explain the reason for possible delay in dilatation of the vessels of one extremity, and in the following experiments attempts were made to determine the causative factors.

Experiment 2 Fig 2 A, 3/2/34, dressed in a tennis shirt and shorts, lay on a couch. At A, after a control period of seventeen minutes, the arms were placed in tanks of water at 44.5°C to 45°C , and at B, at the 87th minute of the experiment, were immersed in water at 11.0°C . At

the commencement of the experiment the temperature of the toes was in the neighbourhood of 14°C . During the control period, the rectal temperature fell slightly (0.03°C). Within six minutes of the arms being placed in warm water the rectal temperature began to rise rapidly. At the 53rd minute of the experiment, 36 minutes after the arms were placed in warm water, the toes commenced to rise in temperature. At this time

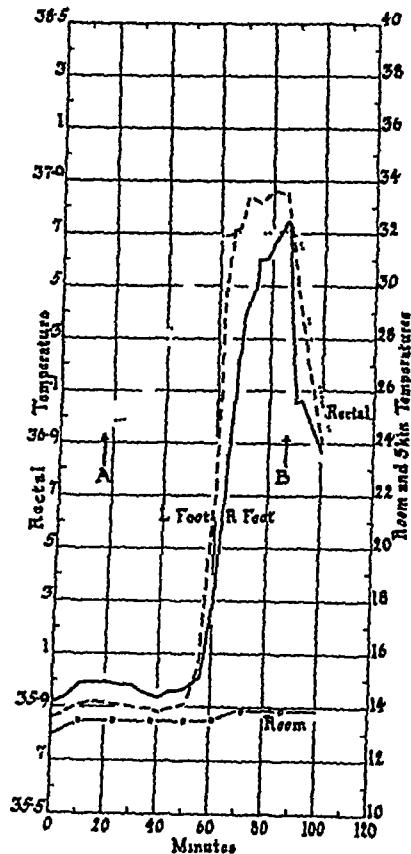


Fig 2

the rectal temperature had reached 37.61°C , a rise of 0.61°C . In this, as in Experiment 1, the room temperature was in the region of 14°C .

This experiment demonstrates that the vessels of both feet of this subject can dilate, and do so in association with a rapidly rising rectal temperature. This is the first point. Secondly, when comparing this experiment with experiment 1 the deduction might be made that the rise in blood temperature, as indicated by the rise in rectal temperature, in experiment 2 is the adequate dilating stimulus—a type of stimulus which was absent in experiment 1.

As a result of these two experiments it is necessary to determine if the rising temperature of the blood is really a stimulus for the production of vasodilatation. To examine this problem three experiments were carried out.

Experiment 3 Fig 3 F T, 6/9/34, a young male adult who had sustained a spinal fracture, causing loss of function below the level of the

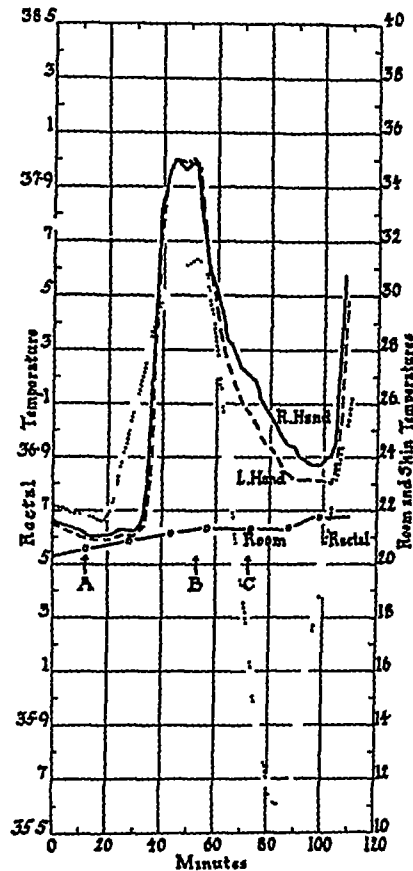


Fig 3

12th dorsal segment of the spinal cord, was the subject. At a later post-mortem examination it was found that below this level, apart from the very tip of the conus medullaris, there was no tissue recognizable microscopically as nervous tissue.

He was subjected to the following procedure. Lying naked on a couch temperature readings were obtained from the tip of the third finger of each hand. Rectal temperature was also taken. At A, after a period for control, his legs were immersed up to the knees in a tank of water at 44.5°C. They

were later transferred at B to water at 9.8°C and ultimately returned at C to water at 44.4°C

During the control period of 12 minutes the rectal temperature gradually fell 0.03°C , from 36.72°C , while the temperature of the fingers kept nearly constant between 21°C and 21.5°C . After placing the legs in hot water the rectal temperature began to rise in $5\frac{1}{2}$ minutes, after $16\frac{1}{2}$ minutes, at which time both fingers warmed up simultaneously, the rectal temperature had risen 0.60°C . Following the transference of the legs to cold water and, at the same time as the rectal temperature began to fall, the temperature of the fingers commenced to fall. When the fingers had cooled down his legs were again placed in warm water, a rise in the temperature of the fingers followed 28 minutes later. The rectal temperature at the second dilatation of the finger vessels was 0.44°C lower than that at the previous dilatation.

Three points are of interest in this experiment. First, vasodilatation in the hands was produced by warming the legs which had no nervous connection with the rest of the body. Therefore, the dilatation in the hands could only be dependent upon the increase of temperature of the circulating blood. Secondly, vasoconstriction occurred on placing the feet in cold water. Thus the falling temperature of the blood produced vasoconstriction. Thirdly, the second vasodilatation occurred when the temperature of the blood was at a lower level than at the time of the previous dilatation.

Experiments 4 and 5 McK, 31/1/34, 11/4/34, a young adult with a spinal fracture and evidence of rupture of the cord at the level of segment D12, was subjected on two occasions to the procedure used in experiment 3. Each time dilatation of the vessels of the fingers occurred only after the rectal temperature had begun to rise. In the second experiment when, after cooling, warming up was again carried out, dilatation of the vessels of the fingers occurred when the rectal temperature was 0.15°C lower than with the first dilatation.

These two experiments uphold the view that the heating of the blood plays a part in bringing about dilatation of the vessels of the hands.

From a study of experiments 2, 3, 4 and 5, it is seen that the method of immersion has always produced dilatation of the vessels of the digits under examination. This has been confirmed by very many experiments in healthy adults. Thus this method appears the better method for causing vasodilatation. Also experiments 2, 3, 4 and 5 demonstrate that a rise of blood temperature is associated with vasodilatation. The presence of any local condition accounting for the delay in one foot, as in experiment 1, remains to be determined. That this delay was no mere isolated occurrence is rendered clear by the following description of other experiments. In these a delay in vasodilatation was found in one or other limb when the hot air bath was applied as the method for the production of vasodilatation.

Experiment 6 Fig 4 A healthy young adult, A C, 26/2/34, whose digital vessels dilated normally when the method of immersion was used, was subjected to the following procedure. He was kept lying under blankets with hot water bottles for 32 minutes, the face alone remaining exposed. During this period the rectal temperature fell from 37.04°C to 36.77°C . The hot water bottles and blankets were removed at A and a fall in temperature of both hands and feet was recorded and the rectal temperature

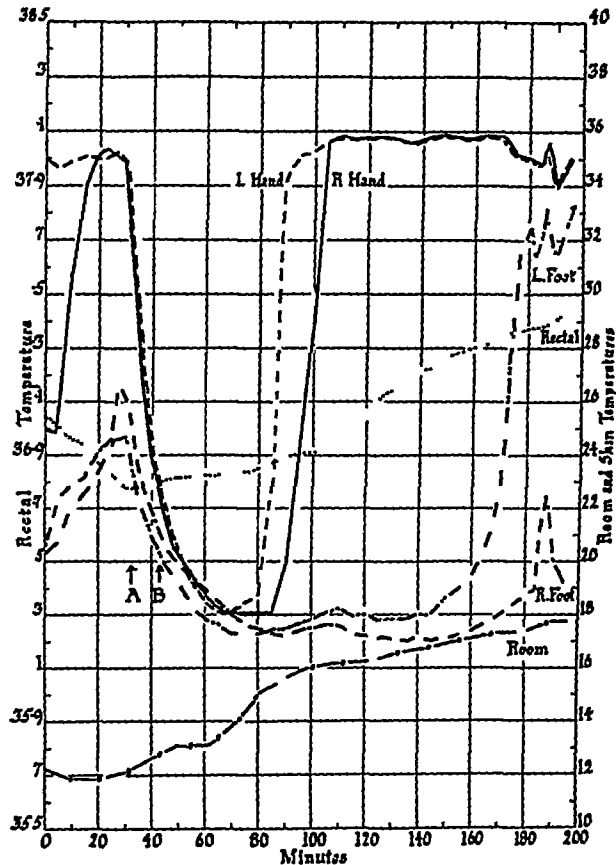


Fig 4

caused to fall. Eleven minutes later, at B, when the temperature of the fingers and toes had fallen to between 20°C and 21°C , the hot air bath was applied. Thirty-eight minutes after the application of this form of heating the left finger warmed up, to be followed five minutes later by the right finger. During this period there was a rise of rectal temperature of 0.08°C , but after the rise of temperature of the fingers the rectal temperature commenced to rise more rapidly until the 164th minute of the experiment, when the temperature of the left toe rose. This occurred 121 minutes after the application of the hot air bath. At the end of the experiment

(192 minutes) the right toe had not risen in temperature apart from an ill-sustained rise to 22.5°C a few minutes before the termination of the experiment

This experiment shows clearly the delay which may occur in dilatation of the vessels of individual limbs, and also how in the upper limb a delay may occur as well as in the lower limbs. This delay occurred in spite of the fact that the hot air bath had reached a temperature of 51.0°C

A second subject was similarly investigated on four different occasions using the hot air bath as the method of warming. In one experiment the

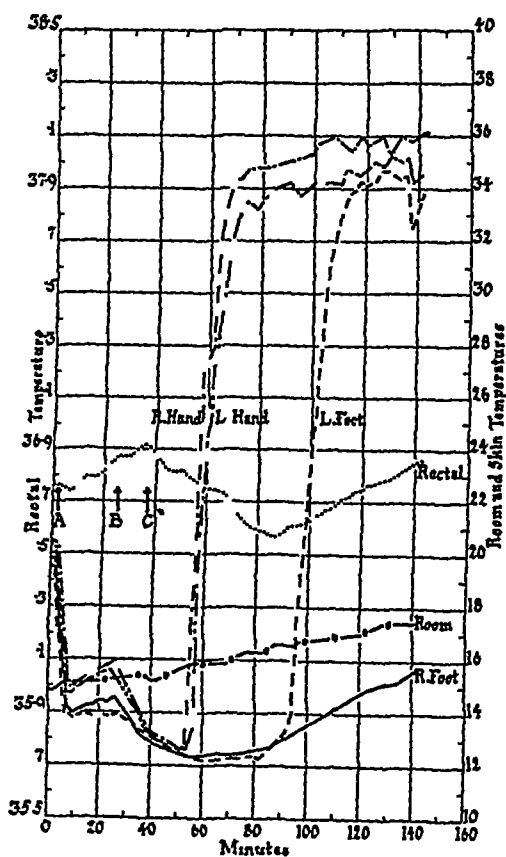


Fig 5

vessels of the digits of the two lower limbs dilated together, thus demonstrating that there was no abnormality of the vessels of the toes. A lack of synchronicity of dilatation of the vessels of the toes was established in the other experiment. The following is a representative experiment.

Experiment 7 Fig 5 M, 26/10/33, was subjected to the following procedure. At A the hands and feet were placed in cold water. At B they were taken out and dried. During the period of immersion the rectal

temperature rose from 36.76°C to 36.87°C. On applying the hot air bath at C there was a considerable fall in rectal temperature, and 16 minutes after its application both fingers rose in temperature. This rise in digital temperature was followed by a more rapid fall in rectal temperature which gradually lessened and began to rise 35 minutes after the rise in finger temperature. Four minutes after the rectal temperature began to rise the temperature of the left toe rose. Fifty minutes later, at the end of the experiment, the right toe had shown no sign of warming, and at this stage the experiment was terminated.

This experiment shows an increase in fall of rectal temperature following dilatation of the vessels of the hands. It also shows that the dilatation of the vessels of the hands may occur with the rectal temperature actually falling. It confirms a previous observation that the vessels of one or other foot may show delay in dilating. From this experiment it is apparent that a rise in rectal temperature associated with immersion of the hands and feet in cold water may occur.

In the four experiments on this subject, the order of dilatation of the vessels of the feet varied though in one experiment the vessels of both feet dilated together. These experiments offer strong evidence that the method of the hot air bath is not a satisfactory one for causing dilatation of the vessels of the lower limbs, and any delay in the dilatation on one side need not necessarily indicate a defect of conduction in the central or peripheral nervous system, or a gross pathological change in the blood vessels.

Two further experiments demonstrate clearly the lack of concurrent dilatation of the limb vessels when the hot air bath is used. In the previous experiments attention has been chiefly paid to the temporal relationship between events of dilatation in the feet, but in the following experiments the lack of unity of behaviour of the vessels of the hands, capable of showing synchronous vasodilatation, will be demonstrated.

B S, a young female adult who had been admitted to hospital for occasional headache which was not the result of any demonstrable organic condition was the subject of two experiments. In one it was demonstrated that the vessels of similar limbs dilated synchronously. In the second experiment the vessels of the fingers of the two upper limbs dilated at different intervals following the application of the hot air bath. The following description of the experiment shows this.

Experiment 8 Fig 6 B S, 16/12/33. During the early stages, while covered with blankets, apart from the head, the rectal temperature fell. Twenty-six minutes from the commencement of the experiment, with the subject still covered, the rectal temperature began to rise. Five minutes later, on removing the blankets at A the rectal temperature rose more steeply, while that of the digits fell. The hot air bath was then applied and turned on at B. At the end of five minutes the right finger became warm, while the rectal temperature was rising, but the left, though it rose in temperature slightly, ceased to warm, and did not do so fully till 60

minutes later. Following the dilatation of the vessels of the right finger the rectal temperature fell 0.15°C in 30 minutes. Subsequent to the fall in rectal temperature a rise commenced and 25 minutes after the rectal temperature had risen the left finger began to warm. Thirty-seven minutes later a rise in the temperature of the toes occurred, then a fall, and finally a rapid rise to 33°C .

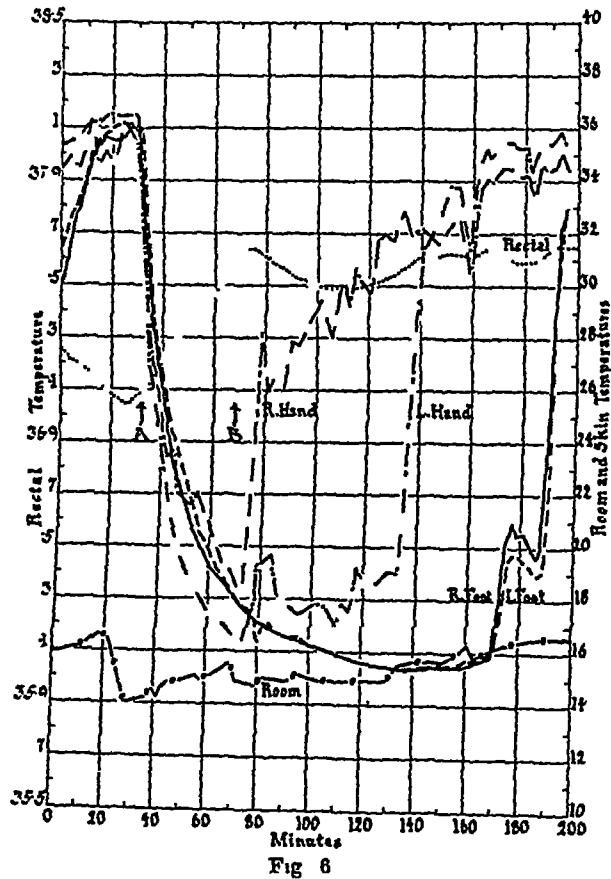


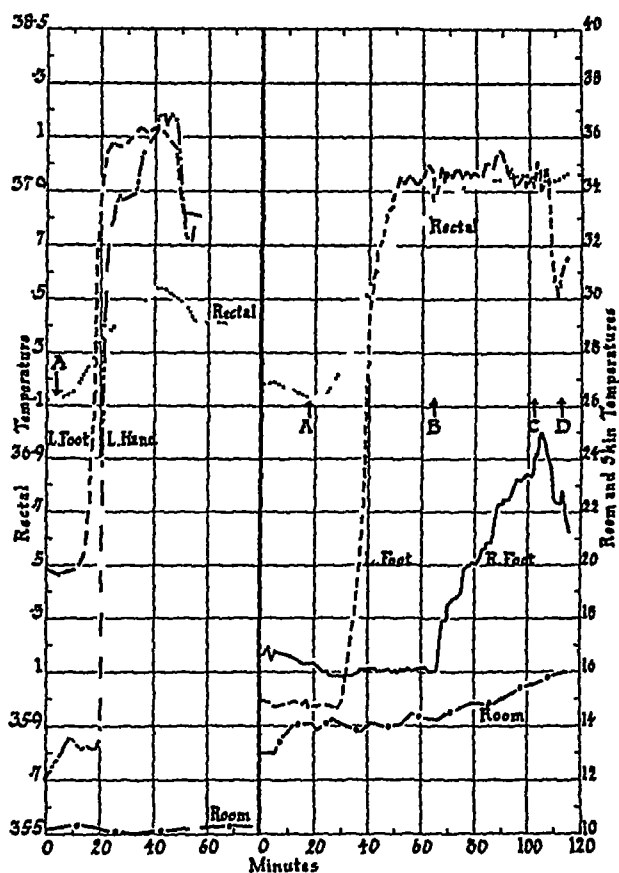
Fig 6

The experiment demonstrates the rise in rectal temperature which may occur on exposure of the body to cool air. This had also occurred in the other experiment on this subject. It further shows the delay in dilatation of the vessels of one hand which from a previous experiment were known to be capable of dilating synchronously with those of the other.

In considering the effect of local conditions upon the time of onset of vasodilatation in a limb the work of Lewis and his collaborators should be referred to. Lewis and Pickering (2) established that there was a delay in vasodilatation of the colder limb. Several experiments were undertaken to amplify the observations of Lewis and his collaborators.

Experiment 9 Fig 7 A C, 15/2/34, placed the left hand in a loosely fitting rubber glove in a basin of cold water at 12°C , for ten minutes, so that the temperature of the hand was 8°C colder than the foot of the same side. The limbs of the opposite side were placed in warm water at 45°C at A, and within 9 minutes the temperature of the toe rose, to be followed 6 minutes later by that of the gloved finger.

Experiment 10 Fig 8 A C, 1/2/34, while lying on his back raised his right leg on a support so that the big toe was 76 cm higher than the left



Figs 7 and 8

big toe. The arms were then placed in warm water at A and an adequate rise in rectal temperature was obtained. The left toe showed a rise in temperature 14 minutes after immersion of the arms in water, but 35 minutes later the right toe still remained at a low temperature. The right leg was then lowered at B to the horizontal level, within two minutes the toe began to warm slowly, and 40 minutes later had only reached a temperature of 25°C , the left toe then having a temperature of 35°C . Both legs were

then raised at C, when a fall in the temperature of the two toes occurred in spite of a continued rise in rectal temperature. Six minutes later, at D, the feet were lowered to the horizontal. The left toe immediately began to rise in temperature, but the temperature of the right toe continued to fall.

These two experiments demonstrate the effect of local conditions on the time of onset and character of vasodilatation, posture and initial temperature being of great importance.

Discussion

From the experiments recorded several deductions may be made. Since the rectal thermocouple was situated 5 cm or more above the anal sphincter it may be assumed that the temperature recorded here closely indicated the temperature of the blood circulating to the deeper tissues of the body. Accordingly it will be accepted for the purpose of this discussion that the rectal temperature indicated the arterial blood temperature and in all probability the temperature of the blood going to the central nervous system. There is not sufficient evidence to state that the rectal temperature represents accurately the actual arterial blood temperature, it may safely be assumed, however, that the rectal temperature, as recorded in these experiments, indicates the time and character of the variations of the arterial blood temperature. The variations found in the rectal temperature in these experiments raises the question as to the accuracy of this method of temperature registration. Care was taken throughout these experiments to avoid any extraneous factor which might affect the registering system. The possibility of a leakage of current from the hot air bath to the system was carefully controlled and all the wires were insulated throughout. The temperature of the digits indicates the volume of the blood-flow in the digit required to maintain the digit at any given temperature. The greater the flow of blood through a digit the higher the temperature of a digit. Consequently a rise in temperature of the digit, and *vice versa*, indicates vasodilatation and vasoconstriction respectively.

The alteration of the rectal temperature associated with the various manipulations deserve attention. In subject S (Fig 6) on two occasions, exposure of the body to cold air was followed by a definite rise in rectal temperature. Similarly, in subjects A C (Fig 4) and A (Fig 1), on exposing the body to the room temperature, there was a slight rise in rectal temperature. Similar observations were made by Laebermeister (3). A complete explanation of this rise in rectal temperature is not at this moment possible as this aspect of the work has not been fully investigated. However, it is possible that the general vasoconstriction produced by the cool air retards the heat loss from the skin thus bringing about a conservation of heat in the body with a consequent rise in rectal temperature. Laebermeister believed that exposure increased the metabolism of the body. The increase of rectal temperature in experiment 7 (Fig 5) when the hands and feet without previous warming were placed in cold water for a short period, may be caused

in this way, especially as this procedure produces a more profound general surface vasoconstriction than exposure to cool air

It will be noted that in two experiments (Figs 1 and 5) when the hot air bath was used, vasodilatation in the hands occurred during a fall in rectal temperature. It is only possible to assume that some factor other than a rising blood temperature was the cause of this. As the nature of this factor is uncertain, it would appear inadvisable to adopt the method of a hot air bath as an experimental means of producing vasodilatation, more especially in the presence of lesions of the central nervous system. Further, as in normal individuals dilatation of the vessels of the hands or of the feet may not be simultaneous when a hot air bath is used, the method of the hot air bath is an inadequate one for the study of possible disorders of the vasodilating mechanism in patients with disease of the nervous system.

Two questions remain. Is there any explanation for the apparent delay in the vasodilatation of one limb? Is there an efficient method by which vasodilatation may be constantly established in normal individuals apart from the blocking of the sympathetic nerves by local anaesthetics?

Gibbon and Landis (1) have shown that vasodilatation may be constantly obtained in normal subjects by immersing a limb or limbs in hot water, and our experience confirms their observations. Pickering and Hess (5), however, record an instance of failure to obtain vasodilatation in the feet in an apparently healthy subject by this method. By testing this method in patients in whom a spinal fracture had damaged the spinal cord, using the legs for immersion it has been demonstrated that vasodilatation occurs in the upper extremities. Gibbon and Landis had previously shown that, in a patient with transverse myelitis, vasodilatation of the hands followed immersion of the legs in water at 43°C. The experiments recorded here, therefore, confirm their contention that in the absence of a nervous pathway the vasodilatation in the upper limbs must be dependent upon a change in the temperature of the blood circulating from the lower limbs. That the rising temperature of the blood is an effective stimulus—probably the most effective—is apparent from a study of the charts from such cases, of which Fig 3 is a typical example. Pickering (4) from his experiments, in which rectal temperatures were taken, believed that the rise in temperature of the blood was the important factor. It is possible that in addition to the alteration in blood temperature an alteration in blood chemistry may be a factor, but on this we have no observations. Accepting a rise in blood temperature as the factor bringing about vasodilatation, the steepness of this rise is possibly of importance. Experiments 1 and 2 suggest that this is so because in Experiment 2 the gradient is steeper than in experiment 1. In the former, the vasodilatation in the feet took place more promptly than in the latter, although the initial temperature of the limbs and room temperature were approximately the same in both experiments. These two experiments alone are cited from our records which yielded many similar results. The importance of the blood temperature gradient is again evident when reference

is made to the charts of cases heated by the hot air bath. In all, the gradient of rise was low, and vasodilatation was irregular. Thus slow rise in blood temperature offers an explanation of the inadequacy of the hot air bath for producing vasodilatation.

Apart from the gradient of rise of blood temperature being of importance in bringing about vasodilatation, the actual temperature of the blood is of importance only when the hot air bath is utilized. The higher the blood temperature, the easier it is to produce vasodilatation. However, when the method of immersion is adopted the actual temperature of the blood is of less importance and vasodilatation may be produced at different temperatures of the blood, provided the gradient of rise is sufficiently steep. This again points to the importance of the steepness of the gradient. The method of immersion is of further interest since, by the transference of the limbs from warm to cold water, it is possible to produce a cooling of the blood and a vasoconstriction. In fact vasodilatation and vasoconstriction may be produced as required. Although it is not our purpose here to discuss the best method of testing the function of the sympathetic system, it is apparent that vasoconstriction is more important to observe than vasodilatation. Vasoconstriction is indicative of the activity of the sympathetic system. Vasodilatation in the limbs can only be taken to result from inhibition of vasoconstriction as the evidence in favour of vasodilator nerves to the vessels of the skin is unsatisfactory or unconvincing. In a future paper observations on vasodilatation and vasoconstriction in limbs of patients with isolated lesions of the nervous system will be recorded and discussed.

Although the inadequacy of the gradient of blood temperature has been suggested as explaining the lack of synchronicity in vasodilatation in two limbs other considerations are worthy of scrutiny. In favour of the inadequacy of the gradient of blood temperature rise are the observations that, following the dilatation in the hands, the blood temperature falls. Presumably the vasodilatation is carried out by the body to increase heat loss in order to keep the blood temperature nearly constant. Thus fall in blood temperature after the vasodilatation in the hands was observed in several of the experiments described. It is possible that by the dilatation of one further limb, the blood temperature may be kept thereafter nearly constant, or the rapidity of rise of temperature of the blood reduced. Experiment 1 suggests this. It is difficult, however, to accept that such a delicate method of blood temperature adjustment is available, for it demands an anatomical basis which has as yet not been demonstrated by either anatomists or physiologists. Lewis and Pickering (2) have drawn attention to the fact that local conditions have a marked effect upon the time of onset of vasodilatation. Thus in considering the results obtained in the presence of lesions of the nervous system it is necessary to take into consideration these observations of Lewis and his collaborators. That this local factor is of importance is demonstrated in experiment 9 when the hand, after being made cooler than the foot, showed vasodilatation after that of the foot.

Besides pointing to the importance of the local factor it upholds the view of Pickering and Hess (5) that the sequence of dilatation in face, hands and feet is probably dependent upon this local factor and not on any central mechanism. Under local factors must also be mentioned that of posture. Experiment 10 demonstrates this clearly. A lack of similarity in posture due to lesions of the nervous system may prove a factor in producing a lack of synchronous dilatation in the limbs of the two sides.

CONCLUSIONS

1 Time of onset of vasodilatation is dependent upon local temperature of a limb, the posture of a limb and the rapidity of rise of blood temperature.

2 A hot air bath produces only a low gradient of blood temperature rise.

3 Immersion method produces an adequate gradient sufficient to overcome local conditions apart from severe changes in posture.

4 The time of onset of vasodilatation in limbs of a subject whose blood temperature is not rising rapidly should not be accepted as an indication of disturbance of the nervous mechanism.

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OBSERVATIONS ON THE CAUSES OF OEDEMA IN CONGESTIVE HEART FAILURE

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THE evidence that oedema fluid is a simple filtrate of plasma has been reviewed briefly by the author in previous papers (1, 24) If oedema fluid is a simple filtrate of plasma there are certain factors which are bound to influence the passage of fluid into and out from blood vessels Firstly there is the effective capillary pressure, which is the capillary pressure minus the mechanical resistance of the tissues Secondly there is the effective colloidal osmotic pressure of the plasma which is the colloidal osmotic pressure of the plasma minus the colloidal osmotic pressure† of the oedema fluid The rate at which the fluid enters or leaves the blood vessels depends also upon a third factor the capillary permeability to water and crystalloids

The purpose of this investigation is to study the factors which affect the passage of fluid through the capillary blood vessels in normal subjects and in cases of congestive heart failure, so as to ascertain the conditions which lead to the development of oedema in the heart failure cases For convenience in presentation of the subject the factors will not be discussed in the order in which they are enumerated above

The effects of changes in the output of urine and of alterations in salt metabolism have an influence upon the accumulation of oedema fluid but are not a subject for discussion in this paper

1 THE EFFECTIVE COLLOID OSMOTIC PRESSURE OF THE PLASMA

It has been explained already that the effective C O P of the plasma is equal to the C O P of the plasma minus the C O P of the oedema fluid

(a) The colloid osmotic pressure of plasma in health and in congestive heart failure

The plasma C O P's of 6 normal subjects were measured directly (24) and were found to be 39, 34, 37, 36, 37 and 37 cm of water, and in 7 subjects

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† Colloid osmotic pressure = C O P

with congestive heart failure with oedema were 29, 26, 23, 29, 38, 26 and 30 cm of water. Blood had not been removed recently from any of the subjects. Similar differences between the plasma C O P in health and congestive heart failure are reported by almost all who study the subject. The fact that almost all of some twenty observers report that the albumin and globulin percentages in plasma are substantially lessened in most cases of congestive heart failure is evidence in the same direction. This last point has been confirmed recently by Thomson (25). An idea of the magnitude of these differences between the plasma C O P in health and congestive heart failure is obtained from Fig 1. It will be seen that in congestive

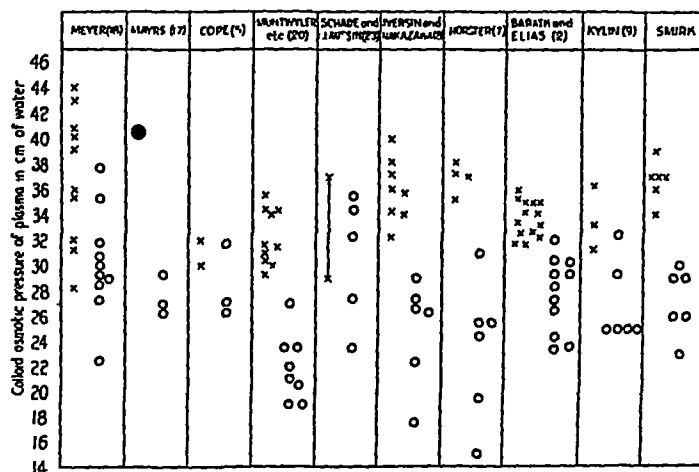


Fig 1 The colloid osmotic pressure of the plasma in health and congestive heart failure
A cross marks the value in a normal subject
A white circle the value in a case of congestive heart failure
A black circle, the average of several values obtained from normal subjects

heart failure the plasma C O P may be near to normal or much depressed. Where the clinical details have been reported it is also clear that values near normal are more frequent in cases with little oedema and, that low values are usual if the oedema is severe. Furthermore, P Meyer (19) has shown with the utmost clarity that clinical improvement in cases of congestive heart failure is accompanied by a return of the plasma C O P towards normal. The degree of this increase in plasma C O P during clinical improvement averaged 7 cm of water in 10 experiments. As the fall of plasma C O P in heart failure depends on the severity of the failure the values obtained by the various observers must depend upon their selection of clinical material. It is seen (Fig 1) that the average degree of difference in the plasma C O P's between groups of normal and of heart failure subjects irrespective of their severity is usually in the region of 6 to 10 cm of water. Individual cases of heart failure may present values which are 15 to 20 cm below the average

for healthy subjects Unfortunately while the above relationship between the plasma C O P's in health and in congestive heart failure is described by almost all observers, the actual values obtained for the plasma C O P differ from one observer to another By some the average normal plasma C O P is thought to be 30 cm of water, by others 40 cm of water Most, including the present writer, find the average normal value in the region of 36 cm of water For this reason the normal values obtained by one technique should not be compared with the values in congestive heart failure obtained by another technique But wherever the relationship is studied using the same technique throughout the experiments there is a fair correspondence between the plasma C O P as measured by the osmometer and as calculated from the percentages of albumin and globulin in the plasma

(b) *The colloid osmotic pressure of oedema fluid in congestive heart failure*

The C O P in œdema fluid is determined in the same way as it is in plasma except that the correction for dilution or concentration of the plasma colloids during dialysis is omitted With œdema fluid this correction is

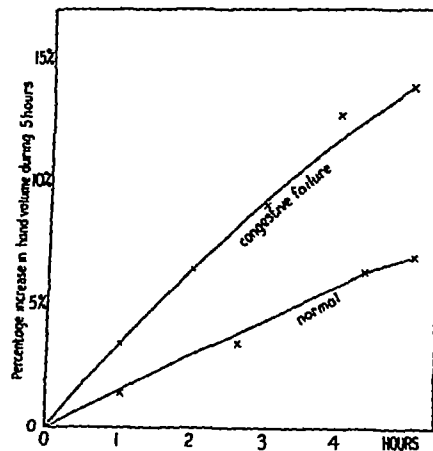


Fig 2 Rates of swelling of hands with artificial venous congestion The congesting pressure was 58 and 60 cm water in the heart failure and normal case respectively

small and may be neglected The C O P of samples of œdema fluid removed from cases of congestive heart failure is usually between 2 and 6 cm of water The actual values in 5 cases are 1.5, 3.0, 6.9, 4.7, 3.3 cm Similar values are obtained by other observers The low C O P in plasma and the presence of a C O P in the œdema fluid both reduce the effective colloid osmotic pressure of the plasma My own results and those of other workers indicate that the fall in effective plasma C O P may be only a few cm or as great as 18 cm of water The average fall is about 11 cm of water

If œdema fluid is a simple filtrate of plasma the fall in the effective C O P of plasma must further the development of œdema by lessening reabsorption We must next consider whether a fall of 10 or 15 cm of water

in the effective C O P of plasma is of itself sufficient to cause œdema I have confirmed what is already a well known fact, that apart from congestive heart failure one may have a fall in the C O P of plasma of 10 or 15 cm of water below the normal without œdema developing even when the patients are allowed to adopt the standing posture (8, 9, 10, 11, 13) This is most evident in cases of malnutrition, after hæmorrhage, in nephrosis and sometimes though less often in the nephrotic stage of glomerulo-nephritis Therefore, we may deduce that the fall in the effective C O P of plasma in congestive heart failure is usually insufficient, of itself, to ensure the development of œdema

2 THE PERMEABILITY OF THE CAPILLARY BED IN THE ARMS OF NORMAL SUBJECTS AND OF SUBJECTS WITH CONGESTIVE HEART FAILURE

We must next consider whether the capillaries in congestive heart failure and in health are equally permeable to water with its dissolved crystalloids This is done by comparing the rates of passage of fluid out from blood vessels under equal filtration pressures In order to equalise the effective filtration pressures it is necessary to correct for the lower plasma C O P in the cases of congestive heart failure Sphygmomanometer cuffs are placed round the arms of normal and heart failure subjects In each case the cuffs are inflated to a pressure which is equal to the measured plasma C O P of the case plus an arbitrarily chosen pressure of 20 cm of water In this way the venous pressure is raised to such a level in each experiment that the difference between the venous pressure in the arm and the plasma C O P is the same in all instances namely 20 cm This increased venous pressure is maintained for 5 hours and causes swelling of the arm both in the normal and in the heart failure subjects The amount of swelling is measured by a simple plethysmograph, which has been described in a previous paper (24)

Results showing the hourly increase in the hand volume are shown in Fig 2 The lower curve is from the normal, the upper curve is from congestive heart failure Increases in hand volume expressed in cc per 100 cc of hand per 5-hour periods are 6.6, 6.4, 6.0, 6.0, 6.4, 3.8, 5.0, average 5.7 in the normal subjects and 9.2, 9.4, 7.0, 13.6, 14.6, 14.4, average 11.4 in the patients with congestive heart failure (Fig 3) Evidently the capillary bed as a whole is more permeable in the hands of cases of congestive heart failure than in health because in the same period of time, under similar pressure conditions it lets through more fluid

During the period of congestion the skin temperatures of the hand and arm were measured by a thermopile and were usually 3 to 6 C less in the cases of congestive heart failure It is to be expected that the increases in the transudation rates in cases of congestive heart failure would be greater if their skin temperatures had been raised to that of normal subjects (6, 12) Moreover in attempting to secure equal effective filtration pressures we correct for the lower plasma C O P in the cases of congestive heart failure

by congesting the hands at a lower venous pressure than in the healthy controls. By mechanical stretching of capillaries (and perhaps by opening up more capillaries) an increase in venous pressure is apt to increase both the surface area of the capillaries available for filtration and their permeability. The degree of artificial venous congestion is less in the heart failure cases, consequently the surface area and permeability of the capillary bed in heart failure will not be increased so much *by the artificial congestion* as in healthy subjects where the degree of congestion is less. Thus the correction we apply for the plasma C O P difference is an over-correction which tends to minimise existing differences in the rates of œdema formation. These considerations serve to emphasise the fact that the capillary bed as a whole is more permeable in the cases of congestive heart failure than in health.

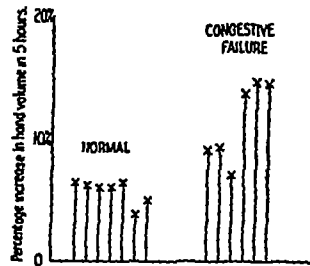


Fig 3 Rates of swelling of hands under equal effective filtration pressures

If instead of applying a correction for the plasma C O P we apply equal degrees of venous congestion to the hands, the increased transudation rates in congestive heart failure cases measure the combined effects of a fall in plasma C O P and an increase in permeability of the capillary bed as a whole. As venous pressures are equal in this experiment the mechanical effects of the venous pressure upon the capillaries are more comparable than in the previous experiment where the pressures were unequal. Using equal venous pressures the increase of the transudation rates in patients with congestive heart failure is greater. With a uniform pressure of 60 cm of water in the sphygmomanometer cuffs the transudation rates were 71, 50, 59, 39 c c per 100 c c of hand per 5-hour period in the normals and 16, 3, 20, 4, 14, 3, 16, 5, 10, 2, 11 c c per 100 c c of hand in the subjects with congestive heart failure. If the average transudation rate is called 100% in the normal it is 200% in the experiments where a correction is applied for the low plasma C O P and 260% in the experiments where no such correction is made.

It is concluded that the permeability of the capillary bed as a whole to water and crystalloids is increased in the arm in cases of congestive heart failure and, if the increased permeability of the arm capillaries is an indication of a general increase in the permeability of the capillaries then this increase must further the development of œdema. The fact that œdema fluid taken from the legs of heart failure subjects contains more protein than the

fluid from cases of hunger cedema and nephrosis in man and of plasmapheresis cedema in animals suggests that the blood vessels are more permeable to protein in congestive heart failure than in these other conditions. If the permeability of blood vessels is increased to protein it must be increased also to water and crystalloids. From his experimental work on animals Bolton (3) suggested that increased permeability of the capillaries may play an important part in causing the cedema of congestive heart failure. These observations on man confirm Bolton's deductions.

3 THE EFFECTIVE CAPILLARY PRESSURE

(a) *Introduction*

It has been explained already that the effective capillary pressure is the capillary pressure minus the mechanical resistance of the tissues to distension. If cedema fluid is a simple filtrate of plasma then a rise of pressure in a group of capillaries must further the local development of cedema. There is however no single capillary pressure but a range of capillary pressures. So that if we are dealing with cedema of a foot we should consider the entire filtering surface of the capillaries in that foot and, if capillary pressure is to supply us with any useful information we should know how much of the surface is subjected to the higher pressures encountered in arterial capillaries and how much to the lower pressures in venous capillaries. Moreover we cannot assume that the entire surface of the capillary bed is uniformly permeable (21) therefore we should also discover how the capillary pressure is distributed in relation to capillary permeability, for with equal pressures more fluid will pass through the more permeable parts of a capillary. These relationships, however, all rest in obscurity. Hence we believe that, in relationship to cedema, measurements either of individual or of average capillary pressures whether accurate or inaccurate are misleading and have little quantitative significance. Therefore we have concentrated upon the relationship between venous pressure and cedema and have attempted no direct determinations of the capillary pressure. It would seem that there are at least 7 points to be considered in relating a venous pressure increase to cedema formation.

1 There is good evidence that an increase of x cm of water in the venous pressure does not produce an increase of as much as x cm of water in the average capillary pressure.

2 It is probable that the resistance of the tissues to distension increases with increase in venous pressure. This is to be expected as the arm swells owing to an increase in its blood content. Thus the effective capillary pressure tends to be increased by less than the increase of venous pressure.

3 With higher venous and capillary pressures the percentage concentration of the plasma protein rises within the capillaries owing to the greater loss of a protein poor fluid from them. This tends to diminish the

effective filtration pressure by raising the C O P of the plasma of capillary blood

4 A rise in the venous pressure by diminishing the pressure difference between the brachial artery and the large veins will tend to slow the circulation through the arm and other things remaining the same, this will cause the capillary pressure to become more nearly equal to the venous pressure

The above factors will tend to make the rate of transudation of fluid less than would otherwise be expected There are however three other factors which will tend to make the rate of transudation of fluid greater than would otherwise be expected

5 An increase in capillary pressure will increase the surface area of the capillary bed available for filtration, partly by stretching of capillaries and perhaps also by causing capillaries to open which previously were closed

6 The stretching of capillaries will tend to increase the permeability of the capillary bed by thinning of the capillary walls

7 The occurrence of reactive hyperæmia as a result of prolonged venous obstruction (16) will tend to increase the capillary pressure

It is interesting to note that despite all these possible variables Landis and Drury and Jones obtained a straight line relationship between the degree of artificial venous congestion in normal human subjects at rest and the rate of accumulation of œdema fluid This straight line relationship might be interpreted as evidence that œdema fluid is a simple filtrate of plasma and that a balance of the forces of capillary pressure and plasma C O P is largely responsible for the interchange of fluid through the capillary blood vessels The conclusion itself rests already upon a firm foundation and some of the evidence in its favour has been admirably reviewed by Landis himself In view of the large number of variables involved it seems however, to the present writer as also to Landis (personal communication) that the straight line relationship observed by Landis and by Drury and Jones should be regarded as a remarkable coincidence rather than strong evidence in favour of the view that œdema fluid is a simple filtrate of plasma

In the following pages a study will be made of the relationship between venous pressure and œdema, first in subjects who are at rest and secondly in subjects who are not at rest

(b) The pressure in the veins on the dorsum of the foot in the normal and in congestive heart failure in relation to the general venous pressure

So far as the present writer is aware no observations on the relationship between the general venous pressure in heart failure and the pressure in the veins of the œdematous legs have been published hitherto In this section the relationship between the general venous pressure and the venous pressure in the legs is studied in normal subjects and subjects with congestive heart failure

The pressure in the veins on the dorsum of the foot in normal subjects
 The apparatus consists of a sharp medium bore needle A attached to the two way tap B through which it may be connected either with the record syringe C or alternately to the side tube D. This side tube D is connected by a rubber tube E to the glass T-piece F. The vertical limb of the T-piece is joined to a long glass tube G (internal bore 2 mm) which lies in front of a scale H. The remaining limb of the T-piece is joined by a rubber tube I to a glass reservoir J which is closed by sterile wool. The rubber tube I is interrupted by a glass tube K containing a constriction. Pinchcocks are placed at L and M. The apparatus is made sterile and the tubes are filled with 1% sodium citrate and air bubbles are removed from the tubes. The tap B is turned so that the needle A is filled with citrate solution and

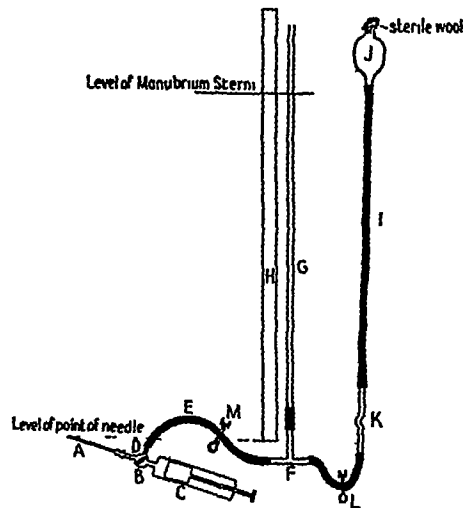


Fig 4

the cocks L and M are then closed. The height of the column of citrate in G should be roughly equal to the expected venous pressure. The tap B is now turned so as to connect A and C and the needle A is thrust into a vein on the dorsum of the foot. Venupuncture in this situation is difficult. The needle is best inserted first through the skin but avoiding the vein and is freed by moving to and fro. The needle is then reinserted through the hole made in the skin and made to enter the vein. There should be a free flow of blood into the record syringe C before the tap B is turned so as to bring the needle A into connection with the manometer. The pinchcock M may then be opened and the zero of the scale H is placed on a level with the point of the needle A. The readings of the manometer are corrected for capillarity and may be taken during as long a period as an hour provided the cock L is opened at intervals of 2 minutes in order to wash out blood

from A, B or D. The capillary leak K prevents a sudden rush of fluid on opening the cock L.

The following experiment is one of 5 which gave similar results

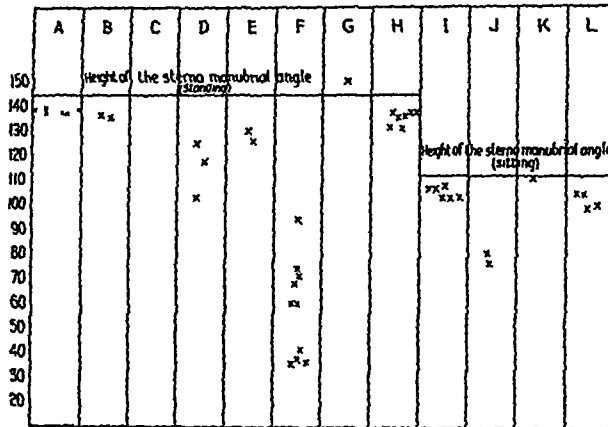


Fig 5 Level of the venous pressure in the right foot under various conditions

Protocol—The needle is placed in the right internal saphenous vein as it arches over the dorsum of the foot. The levels of the crosses shows the venous pressure in various circumstances. The figures for the resting venous pressures A and I are obtained in the time intervals between the performing of experiments B to H and J to L.

Observations in the standing posture

- A The subject stands as still as he is able. The weight of the body is carried equally by the two limbs.
- B The weight of the body is carried by the left leg and the muscles of the right leg are relaxed.
- C The heel of the right foot is raised about a centimetre off the ground and most of the weight of the body is carried on the toes of the right foot.
- D After supporting most of the weight of the body on the toes of the right foot (as in C) the heel is lowered to the ground and the muscles of the right leg are relaxed.
- E The weight of the body is transferred alternately from one foot to the other, the heels being raised about 1 cm from the ground. The knees are not bent.
- F An exercise is performed in which the knees and ankles are alternately flexed and extended at intervals of about three quarters of a second. The exercise is performed in a confined area close to the manometer.
- G Strong expiration with closed glottis.
- H Deep respiration through the mouth.

Observations in the sitting posture

- I The subject is at rest.
- J With the toes resting on the ground the right knee is alternately raised and lowered by extension and flexion of the ankle.
- K Strong expiration with closed glottis.
- L Deep respiration through the mouth.

When the muscles of the leg are stationary and the subject stands upright the pressure of blood at the point of the needle is just a few cm less than the pressure of a column of the citrate solution extending vertically

from the point of the needle to the sterno-manubrial junction. This is true whether the muscles are relaxed by allowing the leg to hang loosely with the weight supported upon the other leg or contracted but stationary. Much more muscle control is required to keep contracted muscles stationary and the least movement which a trained subject can detect in himself will lower the pressure several cm.

When the subject stands with bent knees, or sits, the venous pressure in the foot also changes so that the column of citrate continues to extend to a point which is just a little below the sterno-manubrial angle.

In each posture investigated it has been shown repeatedly that forced expiration increases the venous pressure and, deep respiration increases the amplitude of the respiratory changes in venous pressure making little difference to the average level of the pressure. Exercise of any kind involving the legs decreases the pressure in the foot veins and after exercise ceases, the subject remaining at rest, the level of the citrate then returns to just below the sterno-manubrial junction. These changes in venous pressure with the subsequent return to the resting level show in each experiment that the manometer is responding readily to changes in pressure. The venous pressures in the legs of normal subjects were studied also in the semi-recumbent posture in which the cases of congestive heart failure are examined and the same relationship between venous pressure and hydrostatic pressure is observed in this posture.

The pressure in the veins on the dorsum of the foot in cases of congestive heart failure with oedema of the legs. Clean insertion of a needle into the lumen of a vein in an oedematous leg is difficult. The apparatus is prepared as for the corresponding measurement in the normal foot. The oedema fluid is pressed away until a suitable vein is found and the skin over this vein is anaesthetised with novocaine (without adrenalin). Before making any measurements the shaft of the needle must extend well up the vein and the proper communication of the manometer with the vein must be tested by forced expiration which raises the venous pressure, by upward massage of the leg above the needle which lowers the pressure and by momentary venous congestion which raises the pressure. When it is clear that a proper communication with the vein has been established the venous pressure at rest is recorded with the body inclined at different angles. Several measurements of venous pressure are made in each position. Between each measurement of venous pressure the level of the citrate is raised by allowing citrate to flow in from the reservoir and the excess of citrate in the manometer is allowed to run into the vein until the correct venous pressure is recorded. For each inclination of the trunk the height of the sterno-manubrial junction above the point of the needle in the foot vein is measured. The vertical height above the sterno-manubrial junction of the highest level of pulsation in the neck veins is an index of the height of the general venous pressure. It is found that in the heart failure case at rest the top of the column of citrate comes to within a few cm. of the highest

level of venous pulsation in the neck. The results are summarised in Fig 6. The venous pressure at the point of the needle is usually just a few cm less than the general venous pressure plus the height of a column of citrate extending from the sterno-manubrial junction down to the point of the needle in the foot vein. As in health so in congestive heart failure this relationship is maintained in several postures provided that the subject remains at rest for a minute before and during the measurement of pressure. Thus if the general venous pressure and the vertical distance between the sterno-manubrial junction and the point of the needle in the foot vein are known then at rest the venous pressure at the point of this needle may be calculated. It is clear that at rest an increase in the general venous pressure will produce a corresponding increase in the venous pressure of the foot.

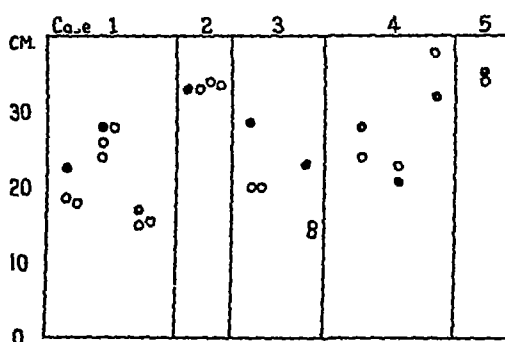


Fig 6 The relation between general venous pressure and the venous pressure in the legs of patients with congestive heart failure

Black circles represent the height in cm of the highest level of pulsation in the neck veins above the point of the needle in the foot vein

White circles represent the pressure recorded in a manometer connected with the needle in the foot vein

The sub groups represent observations made in the same posture

(c) *The effect on oedema formation of a rise in the general venous pressure when the patient is at rest*

When healthy individuals stand as still as is possible for the conscious subject for a period of 1 hour slight oedema of the feet develops. Most of the normal subjects attempting such experiments faint after about 40 minutes immobility in the erect posture. It is therefore impracticable to attempt a similar experiment on subjects with congestive heart failure. Equal degrees of artificial venous congestion in the legs of heart failure and normal subjects cause a greater accumulation of fluid in the legs of the heart failure cases. It seems likely that a high venous pressure in the legs caused by maintaining a state of immobility in the erect posture would give rise to a greater formation of oedema in the heart failure cases. With less complete immobility of the muscles the venous pressure in dependent parts is made less because of the

pumping action of slight muscle movements upon the veins. The lymphatic drainage also is aided by slight muscular movements.

The following observations were made in the hope of deciding whether a rise in the general venous pressure is essential to the development of œdema in cases of congestive heart failure. In congestive heart failure with œdema the general venous pressure measured in relation to the manubrium sterni seldom exceeds 10 cm of water. It is clear from section 3 b that at rest a 10 cm rise in the general venous pressure will produce a rise of about 10 cm in the venous pressure of the legs. If a counter pressure of 10 cm of water is applied to the outside of the blood vessels of the leg in congestive heart failure then the effect of an increase of 10 cm of water in the capillary pressure or in the local venous pressure will be neutralised. If, in such circumstances, œdema continues to form it is clear that the combined effects of the various factors responsible for œdema other than increase in capillary and venous pressure are in themselves sufficient to cause œdema. If, in congestive heart failure a counter pressure of 10 cm of water is applied and the general venous pressure is less than 10 cm of water then the effective venous pressure will be diminished to below the normal level.

In cases where œdema extends up to the knees manometric measurements at the ankle of the œdema fluid pressure show that the counter pressure applied by the œdema fluid itself may be greater than 10 cm of water at a time when œdema fluid is accumulating. Thus in 4 heart failure subjects the pressures of œdema fluid were 10, 12, 4, and 18 cm of water. Therefore, even when the effect of the increase in general venous pressure is counter-balanced by an external counter pressure, the remaining causes of œdema by themselves are sufficient in many cases of congestive heart failure to cause œdema. This may be seen in cases where much œdema accumulates and it is evident that additional fluid has been retained in the body and not merely transported from one region to another. Such instances of the new formation of œdema in the legs, despite the counter pressure of preformed œdema are matters of everyday clinical experience. It may be observed where congestive heart failure develops in a patient who is resting in bed or where œdema re-accumulates after drainage through a subcutaneous incision.

An approximate estimate of the œdema fluid pressure may be gained without the use of a manometer. If a patient with œdema rests in a heart bed with the legs dependent, a horizontal ridge which may be seen and felt usually marks the upper limit of gross pitting œdema. If a hollow needle is inserted into the subcutaneous tissue and is then connected with a vertical glass tube the œdema fluid will rise in the tube to within a few cm of the ridge. If there is no ridge the fluid rises usually to the highest level at which marked pitting œdema of the leg is observed. When œdema extends half way up a leg of average length which is inclined at 30° to the horizontal the vertical height of the œdema above the ankle and therefore the pressure of œdema fluid at the ankle, exceeds 15 cm of water. Œdema fluid has

continued to form after the effect of the rise in general venous pressure has been largely neutralised by the counter pressure of the œdema fluid

Numerous clinical observations support the view that œdema in heart failure cases who are resting is due mainly to causes other than an increase in the general venous pressure. In many patients observed by the author obvious pitting œdema was present over the manubrium and extended up to within 10 cm of the height of the general venous pressure as observed in the veins of the neck. If œdema at this level is to be attributed to an increase in venous pressure then it would be expected that normal people at rest would have œdema of the legs and body up to within about 10 cm of the level of œdema in such patients, for below this the venous pressure would be higher in the normal subjects than in the uppermost œdematous regions of the subjects with congestive heart failure.

In three cases of superior vena cava obstruction the pressure in the median basilic vein was observed to be 18, 31, and 20.5 cm above the level of the sternomanubrial angle without any œdema of the arm or hand being detected. In contrast, œdema of the hands is met commonly in advanced cases of congestive heart failure even where the degree of venous congestion is less than 10 cm, it has been observed frequently by the author with venous pressures of 3 or 4 cm.

It is clear that œdema may develop in cases of congestive heart failure which are resting although the effect of the rise in general venous pressure upon the venous pressure in the legs is neutralised by an external counter pressure. In patients with congestive heart failure œdema may develop in situations where the venous pressure is normal.

(d) The effect on œdema formation of a rise in the general venous pressure when the patient is not at rest

In Section 3 b the effect of movement of the legs upon the local venous pressure of normal subjects is described. Slight movement of the legs caused a fall of as much as 20 cm of water in the local venous pressure and more active movement caused a fall of as much as 100 cm of water. It seemed almost certain that natural walking would produce a fall of at least 50 cm of water pressure. In one normal subject this was verified experimentally by attaching the apparatus drawn in Fig. 4 to belts round the subject's waist and shoulder, inserting the needle into a foot vein and observing the changes in the level of the venous pressure at rest and as the subject walked quietly round the laboratory. It was found that the venous pressure which was 126 cm of citrate solution in the erect posture at rest fell to 60 cm of citrate solution during quiet walking. Patients with congestive heart failure, however, move less actively than normal subjects and their activity is interrupted by many periods of rest. It seems almost certain that the venous pressure in the legs of heart failure subjects is reduced also by exercise. But in congestive heart failure the average degree of this reduction in venous pressure throughout the day will be much less than in the normal subjects.

who are more active and require less rest. Thus the diminished movement of heart failure cases will assist oedema formation by raising the average venous pressure in the legs above the normal. The magnitude of this rise in the average venous pressure is much greater than the rises of general venous pressure which are encountered in congestive heart failure. The diminished movement also will delay the removal of oedema fluid, for the rate of removal of surplus fluid will diminish if the pumping action of the muscles upon the lymphatics is decreased.

The conclusion that the hydrostatic effect of a 10 cm longer column of blood does not by itself cause oedema in subjects who are not at rest may be deduced from the following observations. Short people, about 5 feet in height may get pitting oedema of the ankles when walking if they have heart failure even when the degree of venous congestion is less than 10 cm. Yet tall people about 6 feet in height who are normal do not get pitting oedema of the legs. If we consider the column of blood in the inferior vena cava, unsupported by valves, it is clear that in the 6 foot man the column is at least 10 cm longer than in the 5 foot man and the hydrostatic pressure correspondingly great. Now as far as the legs are concerned it does not matter whether the pressure is high because there is a long inferior vena cava or because there is general venous congestion. Therefore we must draw one of two conclusions. Either the increase of 10 cm in the general venous pressure does not explain the oedema or alternatively the permeability of the capillaries is adjusted normally to the pressure which they have to withstand, permeability being less in the tall than in the short subjects. That this last explanation is not the case was shown by securing equal venous pressures by artificial venous congestion in the legs of 8 very tall and 8 very short subjects, all of them normal, and measuring the rates of oedema formation. For this purpose the technique of Drury and Jones was used. It was found (Fig 7) that with equal venous pressures there was no difference in the rates of oedema formation as judged by the percentage increase in the volume of the legs.

Clinical examples of increases in the venous pressure without oedema are not infrequent in cases where the heart is healthy. Thus Runge (22), Villaret, Sainte-Girons and Salasc (26), and Carulla (4) found a considerable rise of venous pressure, directly measured, in the leg veins of pregnant women. The venous pressure increase was found to be present with the patient in the horizontal and also in the vertical posture. After parturition the venous pressures subsided to normal. Villaret, Sainte-Girons and Salasc found also that a similar increase of venous pressure occurred in the territory of the inferior vena cava in some cases of uterine fibroma and that the venous pressures returned to normal after hysterectomy. The increase in venous pressure averaged about 6 cm of water in the pregnant women in the standing posture and was about 15 cm of water in the few cases of uterine fibroma which have been reported. There is no doubt that increases of even 10 cm of water in the venous pressure augment the rate of transudation of fluid

appreciably (Section 2, Drury and Jones, Landis and Gibbon), but clinical oedema will develop only when the lymphatics are unable to deal with this increased transudation. In a large proportion of the patients studied by the above mentioned authors, no oedema was observed. The average increase in venous pressure in patients without oedema, during the last three months of pregnancy was 14.8 cm of water lying and 9.6 cm of water standing, in Runge's series and 5 cm of water in the cases of Villaret, Sainte-Girons and Salasc. Evidently such increases of pressure in the territory of the inferior vena cava do not ensure the development of oedema in patients who are up and about. Almost invariably 6 cm of venous congestion in patients with congestive heart failure is associated with oedema whether the patient is confined to bed or not.

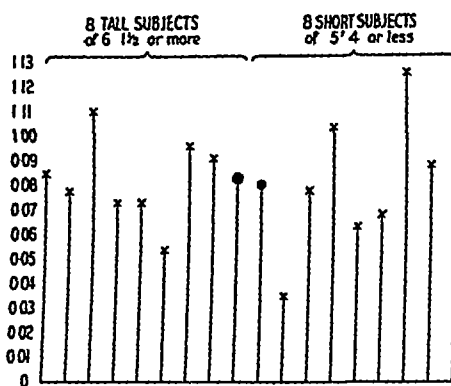


Fig 7 The permeability of the capillary bed in the legs is not related to the height of the subject. Each vertical line marked with a cross represents the increase in leg volume of a normal tall subject over 6 feet 1½ inches in height or of a normal short subject under 5 feet 4 inches in height during artificial venous congestion at a pressure of 85 mm of mercury and at a temperature of 37°C. The measurements are made between the tenth and twentieth minutes of venous congestion. The vertical lines marked with a black circle represent the average increases in leg volume for the tall subjects and for the short subjects. The averages of the measurements of leg volume increases between the twentieth and thirtieth minutes showed a similar equality.

It may be objected that the increases of pressure in the inferior vena cava territory are not quite analogous to the increases in general venous pressure of congestive heart failure for these latter have the additional factor of slight obstruction to the outflow of lymph from the thoracic duct. This objection does not apply to the examples already described of high venous pressure caused by obstruction of the superior vena cava in which there was no oedema.

With increases of 3 to 6 cm of water in congestive heart failure oedema is usually present. Increases of 3 to 6 cm of water without oedema are by no means rare however, when the heart is healthy as judged by its capacity for work. Villaret, Sainte-Girons and Besançon (27) have reported increases

of 3 cm of water in the venous pressure with spontaneous pneumo-thorax and a fall in this pressure after reducing the raised intra-thoracic pressure to atmospheric. In therapeutic pneumothorax the venous pressure was observed to increase by 1 to 8 cm of water and the above authors regard the higher rises of pressure as an indication of danger due to displacement of the mediastinum. The present writer on the basis of about 30 cases without œdema finds increases of 2 to 3 cm of pressure are frequent in the arm veins and in two instances increases of 4 cm were observed using the direct method of measurement already described. The pressure increase was also observed in the veins of the neck using the clinical method described by Lewis (15).

Six cases of hepatic cirrhosis with a fair capacity for exercise and no œdema, four with and two without ascites, had increased general venous pressures of 4 to 7 cm of water without œdema. In a patient with varicose veins but otherwise fit and engaged on hard manual labour in an engineering works the venous pressure measured directly in the arm was 6 cm on the first examination and 5 cm 6 months later. This patient had no history of œdema and no œdema was found on the two occasions when the venous pressure was measured. Slight increases of the general venous pressure without heart failure have been encountered also in massive pleural effusion, emphysema, hyperthyroidism and leukæmia, but such increases are not to be regarded as features of these disorders. It is clear therefore that moderate increases in venous pressure may be present without œdema in cases where there is no evidence of heart failure.

It seems justifiable to conclude from the experimental and clinical evidence that increases of as much as 10 cm in the general venous pressure do not ensure the development of œdema. The almost invariable occurrence of œdema in cases of congestive heart failure with as much as 4 cm of venous congestion indicates that the œdema in congestive heart failure is in a large measure due to factors other than the general venous pressure increase.

In subjects who are not confined to bed the average venous pressure in the legs of heart failure subjects is at a much higher level than in subjects who are active, because movements of the legs produce a large fall in the local venous pressure and the degree of fall is less in subjects whose movements are less active and are interrupted by frequent periods of rest.

(e) The effect on œdema formation of a uniform rise in the capillary pressure apart from the secondary effects of the rise in capillary pressure upon the blood vessels

In Section 3 c it was shown that the rise in local venous pressure which results from increases of as much as 10 cm in the general venous pressure is insufficient to account for the œdema in congestive heart failure. In this we consider the effect of venous pressure upon œdema formation without discussing the problem of whether the œdema which results is due mainly to the increased capillary pressure or is due to secondary changes in the

capillary blood vessels which are the result of the rise of pressure within them. These secondary changes in the capillary blood vessels include increase in the surface area and permeability of the capillary wall and decrease in the rate of blood flow through the capillaries. We do not know whether the combined effects of such secondary actions on the blood vessels assists or resists the development of oedema. It is for this reason that a discussion of the direct effect of a change in capillary pressure upon oedema requires separate treatment.

In the previous sections arguments have been advanced which show that a rise in the general venous pressure will cause a corresponding rise of the pressure in the foot veins and that this rise in local venous pressure will cause a rise of pressure in the local capillaries. The average rise of pressure throughout the capillary bed is less than the rise of venous pressure which causes it. Since in congestive heart failure the rise of general venous pressure is usually less than 10 cm it follows that the rise in the capillary pressure due to the increase in general venous pressure is likewise less than 10 cm. Let us now discuss a hypothetical case in which the rise of capillary pressure is considered in relation to oedema formation apart from its secondary effects upon capillary surface, capillary permeability and other variants.

A fall of 10 cm of water in the plasma C O P will have the same effect upon the effective filtration pressure as a uniform rise of 10 cm in the capillary pressure. On physico-chemical grounds there is reason to believe that the rate of filtration through a simple membrane varies directly with the effective filtration pressure and that it does not matter very much whether a high effective filtration pressure is due to an increased mechanical pressure or to a decreased C O P. It is unlikely that this deduction can be verified by exact experiments for it seems highly improbable that the direct effect of a rise in capillary pressure can be separated from the effect of those changes in the blood vessels which are secondary to this rise in pressure. Now a fall of 10 cm of water in the plasma C O P is insufficient of itself to cause oedema (8, 9, 10, 11, 13, 14), therefore we may think it likely that a uniform rise of 10 cm of water in capillary pressure, apart from its secondary effects upon blood vessels is also insufficient to cause oedema.

MAIN CONCLUSIONS

In congestive heart failure observations have been made concerning certain factors which favour the development of oedema.

- 1 There is a fall in the colloid osmotic pressure of the plasma, and some protein passes through the blood vessels with the oedema fluid. The colloid osmotic pressure of the protein of this oedema fluid has varied between 1.5 and 7 cm of water and this acts in opposition to the colloid osmotic pressure of the plasma. Thus the effective colloid osmotic pressure is reduced

and as a result the reabsorption of fluid back into the blood vessels is decreased

2 At rest the venous pressure in the legs is approximately equal to the general venous pressure plus the pressure of a column of water extending vertically downwards from the manubrium sterni to the situation where the venous pressure is measured. Active muscular movements of the legs diminish the venous pressure in the legs by 10 to 100 cm of water. Thus the incapacity for exercise of patients with heart failure increases the average venous pressure in the legs, throughout the day, to much above the normal. The increase above the normal of the average venous pressure in the legs of heart failure subjects is produced mainly by their muscular inactivity and to a much smaller degree by the increase in general venous pressure. The increases in the general venous pressure in cases of congestive heart failure are not by themselves sufficiently great to cause oedema. All factors increasing the local venous pressure, however, will increase the effective filtration pressure and thus will increase the rate of transudation of fluid out from blood vessels. Conversely the counter pressure of the oedema fluid on the outside of the blood vessels, which is exercised as the oedema accumulates, will decrease the rate of transudation of fluid.

3 The permeability of the blood vessels to water and to crystalloids is demonstrably increased in congestive heart failure and this augments the rate of loss of fluid from the blood vessels. The increase in the permeability of the blood vessels to water and to crystalloids may be such that with equal effective filtration pressures the rate of transudation of fluid in congestive heart failure is twice the normal. Increase in the permeability of the capillaries to water and crystalloids only influences the rate at which loss of fluid from the blood vessels occurs and despite such an increase in capillary permeability, fluid will only leave the blood vessels in situations where the effective capillary pressure exceeds the effective colloid osmotic pressure of the plasma.

4 The magnitudes of the various factors which combine to cause oedema in congestive heart failure differ from case to case. Two of the important causes of such oedema, namely the increase in the capillary permeability and the fall in the colloid osmotic pressure of the plasma, are also partly responsible for the oedema in the nephrotic stage of glomerulo-nephritis.

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4 The magnitudes of the various factors which combine to cause oedema in congestive heart failure differ from case to case. Two of the important causes of such oedema, namely the increase in the capillary permeability and the fall in the colloid osmotic pressure of the plasma, are also partly responsible for the oedema in the nephrotic stage of glomerulo nephritis.

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OBSERVATIONS ON THE HISTAMINE YIELDING SUBSTANCE IN THE PLASMA AND RED CELLS OF NORMAL HUMAN SUB- JECTS AND OF PATIENTS WITH CONGESTIVE HEART FAILURE

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A METHOD for the estimation of a histamine-like substance in blood was published recently by Barsoum and Gaddum (4). The method involves precipitation of the blood proteins by trichloroacetic acid, filtration, treatment of the filtrate with concentrated hydrochloric acid, subsequent boiling for 1.5 hours and evaporation to dryness *in vacuo*. The dry extract is purified further and its histamine equivalent is determined by biological assay on the rectal caecum of the fowl or on the ileum of the guinea pig. There is strong evidence that the substance present in the extract obtained from the blood by means of the chemical treatment mentioned above is histamine (4). This view is supported also by our finding that the histamine-like substance in the blood extracts is destroyed by a preparation containing histaminase. It is not known, however, if true histamine is present in the untreated blood sample.

In this paper the substance in untreated blood which on chemical extraction yields histamine or a substance very like histamine is called histamine yielding substance, (H.Y.S.). The concentration of H.Y.S. in untreated blood is expressed in terms of the histamine equivalent of blood extracts prepared by Barsoum and Gaddum's method. It is still uncertain whether H.Y.S. and histamine are identical. Evidence which indicates that H.Y.S. is active histamine will be mentioned in this paper.

In a previous paper one of us (8) showed that the permeability of the capillary bed to water and crystalloids is increased in congestive heart failure. Barsoum and Gaddum (5) showed recently that in the dog a considerable increase in the concentration of H.Y.S. is found in samples of whole venous blood taken from a limb during reactive hyperaemia following a period of occlusion of the femoral artery. It seemed possible that a more prolonged though smaller decrease in the rate of circulation of blood through a limb due to congestive heart failure might produce also an increase in the H.Y.S. of the venous blood. If H.Y.S. is active histamine an increase in

the H Y S of the blood in congestive heart failure cases might explain the greater permeability of the capillary blood vessels in this condition. On clinical grounds the above explanation of the increase of capillary permeability in congestive heart failure seemed unlikely because as little as 7 or 10 γ * of histamine when rapidly injected intravenously into a normal man causes flushing of the skin of the face. The absence of pathological flushing from patients with congestive heart failure and oedema suggests that there is no appreciable excess of active histamine in the circulating blood of these patients.

The concentration of H Y S in blood was determined by the method of Barsoum and Gaddum (4). The error of the method is about $\pm 25\%$. It was found that the concentration of H Y S in the blood samples was much above the normal in heart failure cases. In 8 normal subjects the concentrations of H Y S in whole venous blood were 0.05 — 0.11 γ per c.c. (average 0.08 γ per c.c.) and in 8 subjects with congestive heart failure the concentrations were 0.08 to 0.30 γ per c.c. (average 0.25 γ per c.c.). If this pathological increase of 0.17 γ per c.c. of H Y S above the normal were produced artificially in the blood of a normal man by intravenous injection of histamine much discomfort would result and there would be marked flushing of the skin vessels, a fall in blood pressure and histamine headache. But despite the high concentration of H Y S in their bloods the patients with congestive heart failure showed no symptoms which might indicate the presence of an excess of active histamine in the blood. Three possibilities are consistent with this apparent inactivity of the H Y S in the heart failure cases. The study of these possibilities forms the main subject matter of this paper.

- 1 The H Y S may neither be histamine nor a substance with a histamine-like action.
- 2 The subjects with congestive heart failure may be less sensitive to histamine than the normal subjects.
- 3 The increase in the concentration of H Y S may be confined to the red cells.

RESULTS

The patients with congestive heart failure selected for the following observations were definite cases, with much dyspnoea on exertion, increased general venous pressure and usually ascites and oedema. The subjects used as controls were members of the laboratory staff or hospital out-patients without serious disability.

1 *Evidence concerning the activity and nature of H Y S*

It has been reported (2) that the H Y S of dog's coronary venous blood is destroyed rapidly when the blood is incubated at 37°C with a preparation

* $\gamma = 0.001$ mg. Quantities of histamine are expressed in terms of histamine base.

containing histaminase The effects of Anrep's preparation of histaminase (1) has now been tested on human blood The concentration of H Y S in a mixture of normal human blood and histaminase was estimated immediately after mixing and also after incubation at 37°C for 1 hour The results show that given time, histaminase destroys H Y S in normal human blood

TABLE I

The effect of a preparation containing histaminase on the H Y S of whole venous blood from normal subjects

Sample	Concentrations of H Y S in γ per c c of blood as estimated by Barsoum and Gaddum's method	
	Immediately after addition of histaminase	One hour after incubation with histaminase at 37° C
1	0 10	0 05
2	0 08	0 04
3	0 08	0 06
4	0 10	0 05

The effect of histaminase on blood samples taken from cases of congestive heart failure was studied also These blood samples contain higher concentrations of H Y S than the normal

TABLE II

The effect of a preparation containing histaminase on the H Y S of whole venous blood from subjects with congestive heart failure

Sample	Concentrations of H Y S in γ per c c of blood as estimated by Barsoum and Gaddum's method	
	Immediately after addition of histaminase	One hour after incubation with histaminase at 37° C
1	0 32	0 08
2	0 20	0 06
3	0 34	0 06
4	0 16	0 05

The H Y S of blood is destroyed by histaminase in the congestive heart failure cases just as it is destroyed also in the blood of normal subjects The fact that the H Y S of human blood is destroyed by histaminase suggests that H Y S may be identical with histamine It is possible that a non-specific histamine destroying enzyme may be the active agent in the "histaminase" preparation used This possibility weakens the evidence

that the histamine like body in blood is histamine but other evidence concerning this question will be submitted later which is not dependent on the specificity of the preparation of histaminase

Although the percentage of H Y S present in 2 c c of human blood is insufficient to produce an appreciable fall in the blood pressure of the anaesthetised cat, the H Y S is present in a higher concentration in tissues. It was found that an extract with distilled water of 2 g of human liver when injected intravenously into an anaesthetised cat caused a fall of blood pressure. If this extract is incubated with histaminase before injection, the fall of blood pressure is less. This result is understood readily if the H Y S in human liver is histamine or another vasodilator substance which is also destroyed by the preparation of histaminase.

To obtain further evidence concerning the nature of H Y S, the effect of histaminase on rabbits' blood was studied. Rabbits' blood was used because it is known to be very rich in H Y S. The concentration of H Y S is about 10 γ histamine equivalent per c c of blood and therefore if all this H Y S is histamine or a histamine-like substance, small quantities of laked

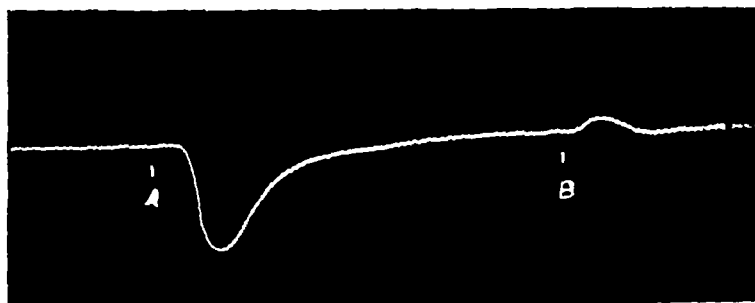


Fig 1 ($\times \frac{1}{2}$) The effect of histaminase on the blood pressure lowering property of laked rabbits' blood

- A Action on the cats' blood pressure of $\frac{1}{3}$ c c of laked rabbits' blood not incubated with the preparation of histaminase
- B Action on the cats' blood pressure of $\frac{1}{3}$ c c of laked rabbits' blood incubated with the preparation of histaminase

rabbits' blood should cause a lowering of the blood pressure in an anaesthetised cat or dog and should cause contraction of a piece of isolated ileum. A sample of laked rabbits' blood was divided into two parts. The first part was incubated at 37° C for 1 hour with histaminase and the other part was incubated under the same conditions without histaminase. The blood which was incubated without histaminase was now mixed with histaminase. Immediately after mixing the incubated blood and histaminase, a portion of the mixture containing $\frac{1}{3}$ c c of the rabbits' blood was injected intravenously into an anaesthetised cat or dog. The effect of this injection was compared with the effect of injecting $\frac{1}{3}$ c c of rabbits' blood which had been incubated with an equal amount of histaminase. It was observed (Fig 1) that the fall in blood pressure on injection of $\frac{1}{3}$ c.c of rabbits'

blood incubated with histaminase was slight. There was, however, a marked fall of blood pressure in the control observations where the histaminase was only added to the blood after the blood had been incubated and immediately before the mixture was injected. Six experiments of this type were performed and similar results were obtained in all of them. It is shown therefore that the preparation of histaminase destroys the substance responsible for the blood pressure lowering effect of laked rabbits' blood and also destroys the H Y S of rabbits' blood as determined by the method of Barsoum and Gaddum.

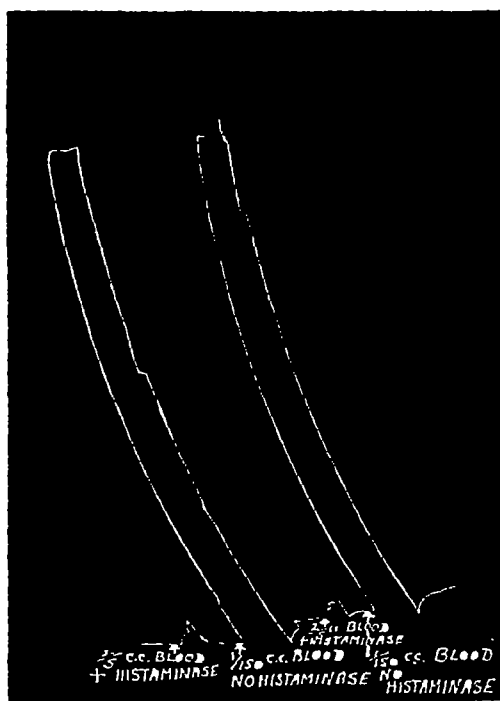


Fig 2 (\times $\frac{1}{2}$) The effect of the preparation of histaminase upon the capacity of laked rabbits' blood to cause contraction of the guinea pig ileum

In all of six experiments it was found that the capacity of laked rabbits' blood to produce contraction of the G P I is almost abolished by previous incubation of the blood with histaminase (Fig 2). These observations make it likely that H Y S is either histamine or a substance closely allied to histamine.

It was shown by Feldberg and Schilf (7) that when a large dose of histamine is applied to a piece of guinea pig ileum there is a prolonged contraction of the ileum. When this contraction passes off, after about 1 hour, the ileum gives no response to the addition of further small doses of histamine. The ileum remains sensitive, however, to other stimulants.

such as acetyl choline, posterior pituitary hormone, barium, sodium hydroxide and distilled water (4) If, therefore, an unidentified substance causes contraction of normal guinea pig ileum but fails to cause contraction of guinea pig ileum which has been treated previously with histamine then it is likely that the unidentified substance is histamine (7, 4) 0.05 γ of histamine was added to a bath containing a short length of atropinised guinea pig ileum suspended in Tyrode solution and the magnitude of the resulting contraction was recorded The bath was now washed out with Tyrode solution and 1/50 c.c. of laked rabbits' red cells (containing

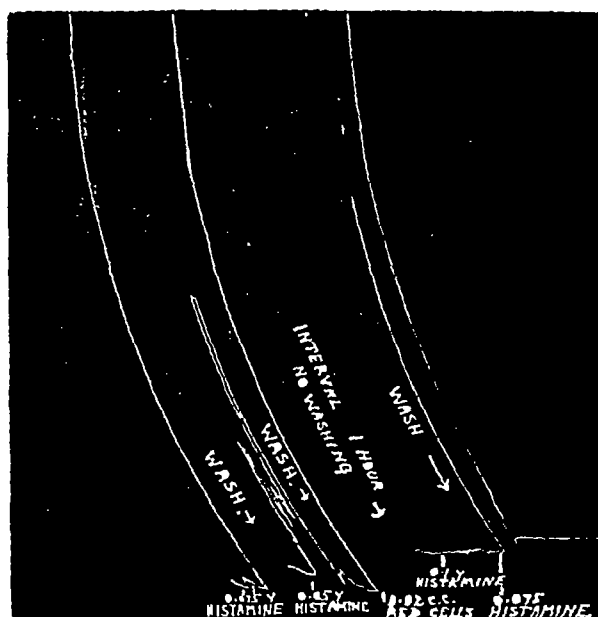


Fig 3 ($\times \frac{1}{2}$) Experiment showing that laked rabbits' red cells desensitise the guinea pig ileum to the action of histamine

approximately 0.3 γ of H Y S) was added A strong contraction of the guinea pig ileum occurred This time the contents of the bath were not removed but after about 1 hour the guinea pig ileum relaxed to its original length 0.1 γ of histamine was now added to the bath and little or no contraction of the guinea pig ileum occurred (Fig 3) This indicates that laked rabbits' blood desensitises the guinea pig ileum to the action of histamine The bath was next washed out and refilled with Tyrode solution and a further dose of 0.075 γ of histamine was added It was found that washing with Tyrode solution had restored the original sensitivity of the ileum to histamine for contraction resulted

Similar experiments were made but with the difference that the reaction of the guinea pig ileum to 1/100 c.c. laked rabbits' blood was tested before and after desensitisation of the guinea pig ileum by 0.25 γ of histamine This shows that the desensitising of the guinea pig ileum to histamine also

desensitises it to the histamine-like action of laked rabbits' blood. The reaction of the ileum to 1/100 c c of laked rabbits' blood was tested again after sensitivity of the guinea pig ileum to histamine had been restored by washing the ileum with Tyrode solution (Fig 4). The sensitivity of the guinea pig ileum to laked rabbits' blood is restored when its sensitivity to histamine is restored. It was found also that on incubation with histaminase, 1/50 c c of rabbits' blood lost its capacity to desensitise the guinea pig ileum to the action of histamine.

It is clear, therefore, that this substance in rabbits' blood resembles histamine in that it has the capacity to desensitise the guinea pig ileum to

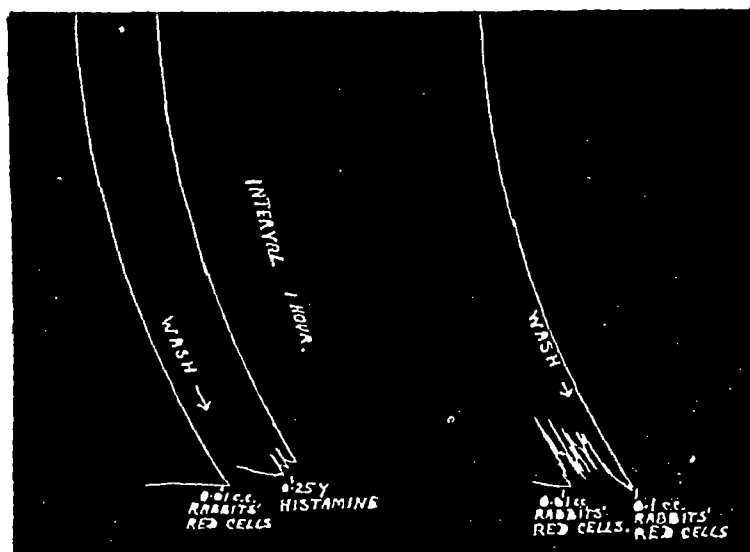


Fig 4 ($\times \frac{1}{2}$) Experiment showing that histamine desensitises the guinea pig ileum to the action of laked rabbits' red cells

histamine, and the capacity of rabbits' blood to desensitise the ileum is destroyed also by the preparation of histaminase.

In the following experiment a comparison is made of the effects of H Y S and histamine upon the blood pressure of the dog. The experiment is designed so that the presence in laked rabbits' blood of depressor substances other than H Y S do not invalidate the conclusions drawn. It has been mentioned already that the intravenous injection of laked rabbits' blood causes a fall in the blood pressure of the anaesthetised cat or dog. If this rabbits' blood is treated first with histaminase the fall of blood pressure produced by intravenous injection of the blood is less. This depressor effect of the blood which has been decreased by the action of histaminase may be restored to its original level by the addition of histamine to the treated blood. The amount of histamine per c c of treated rabbits' blood

which is required for this purpose was determined by trial and error. The amount of H Y S in the original rabbits' blood and in the rabbits' blood after treatment with histaminase was determined by Barsoum and Gaddum's method. It was found that the amount of H Y S destroyed by histaminase (expressed as its histamine equivalent) was approximately equal to the amount of histamine which restored to the treated blood that part of its blood pressure lowering effect which was destroyed by histaminase. Thus H Y S and histamine have approximately equal depressor actions on the blood pressure of the anaesthetised cat or dog. For example, in one of the five experiments performed the histaminase destroyed 14.4 γ per c.c. of the H Y S present in a sample of rabbits' blood as measured by Barsoum and Gaddum's method. 15.0 γ per c.c. of histamine was now added to 1 c.c. of this rabbits' blood which had been treated with histaminase. The 1 c.c. of blood was then injected intravenously into an anaesthetised dog. The

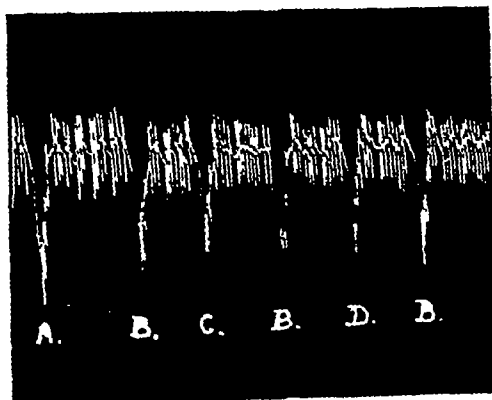


Fig 5 (\times 1) A comparison of the effects of H Y S and histamine on the blood pressure of the anaesthetised dog

- A 1 c.c. of laked rabbits' blood treated with histaminase + 20 γ of histamine
- B 1 c.c. of untreated laked rabbits' blood
- C 1 c.c. of laked rabbits' blood treated with histaminase + 15 γ of histamine
- D 1 c.c. of laked rabbits' blood treated with histaminase + 10 γ of histamine

fall in blood pressure produced thereby was equal to the fall in blood pressure on injection of 1 c.c. of the original laked rabbits' blood untreated with histaminase. The difference between the two blood samples is that 14.4 γ of H Y S present in the original sample has been in the second sample destroyed and then replaced by 15.0 γ of histamine. The effects of intravenous injections of the two samples upon the blood pressure of the anaesthetised dog are equal. This shows that the effects of histamine and H Y S upon the blood pressure of the dog are equal within the error of the experiment. One of the above experiments is illustrated in Fig 5. A comparison was made also between the actions on the guinea pig ileum of laked rabbits' blood and laked rabbits' blood in which much of the H Y S had been destroyed by histaminase and then replaced by an equal amount of histamine.

It was found that amounts of histamine and H Y S which are estimated to be equal by the method of Barsoum and Gaddum produce approximately equal contractions of the guinea pig ileum. Thus the H Y S destroyed by histaminase was found to be 14 γ per c c of rabbits' blood and the amount of histamine required to replace this (as determined by the effect of the blood + histamine on the guinea pig ileum) was 14.4 γ per c c.

2 *Evidence that patients with congestive heart failure react normally to intravenous injections of histamine*

Chemical proof of the identity of H Y S and histamine is lacking but the biological evidence presented in Section 1 shows that H Y S is either active histamine or is an active substance with many of the pharmacological properties of histamine.

TABLE III

The effect of intravenous injections of histamine in normal subjects and patients with congestive heart failure

Histamine	Effect on normal subjects	Effect in congestive heart failure subjects
6.7 γ in 2 seconds	2 subjects gave a slight facial flush and slight acceleration of the heart but no headache 1 subject was unaffected	3 subjects gave a slight facial flush and slight acceleration of the heart but no headache 1 subject was unaffected
33 γ in 2 seconds	Definite flushing and acceleration of the heart and transient headache in all of 3 subjects	Definite flushing and acceleration of the heart and transient headache in all of 4 subjects
13 γ in 1 minute	No reaction observed in 2 subjects	No reaction observed in 3 subjects Slight facial flushing but no headache in 1 subject
20 γ in 1 minute	Flushing of the face but no headache in 3 subjects and no effect observed in 1 subject	Flushing of the face in 3 subjects, one of these being a transient effect. No reaction in 1 subject No headache
33 γ in 5 minutes	No reaction in 2 subjects	No reaction in 2 subjects
33 γ in 2 minutes	Flushing but no headache in 2 subjects	Flushing but no headache in 2 subjects
67 γ in 2½ minutes	Marked flushing but no headache in 1 subject	Flushing but no headache in 1 subject
167 γ in 4½ minutes	Flushing but no headache in 1 subject	Flushing but no headache in 1 subject
333 γ in 9½ minutes	Flushing but no headache in 1 subject	Flushing but no headache in 1 subject

The presence without symptoms of a high concentration of histamine-like substance in the whole blood of heart failure cases requires an explanation. This absence of the symptoms of histamine poisoning might

be explained by relative insensitivity of the heart failure cases to histamine, and this possibility has been tested by comparing the reactions of heart failure and normal subjects to intravenous injections of histamine

With the subjects lying in the recumbent posture, intravenous injections of 6.7 to 333 γ of histamine were made. The rates of injection were varied. The effects of these injections upon the facial colour was recorded together with the times of onset and cessation of headache, whenever this symptom occurred.

The preceding table shows that there is no great difference between the sensitivity to intravenous injections of histamine in normal subjects and subjects with congestive heart failure. It is seen that the rate of disappearance of the flush on cessation of the injection is approximately the same in the heart failure as in the normal subjects. Hence it seems that the rate of disappearance of histamine from the blood is approximately normal in heart failure cases.

It was observed both in heart failure and normal subjects that injections of histamine at a rate of 20 γ per minute produced a flush in about 40 seconds and the flush persisted without increasing until about 5 seconds after stopping the injection, when the flush disappeared.

We may conclude that patients with congestive heart failure react normally to intravenous injections of histamine. Lack of sensitivity to histamine in heart failure cases cannot be advanced, therefore, as an explanation for the absence of a physiological reaction to the abnormally high whole blood histamine found in such cases.

3 *The significance of the distribution of H Y S between the plasma and red cells*

It is clear that the H Y S in blood is a substance with histamine-like properties and that the subjects with congestive heart failure are not insensitive to the pharmacological action of histamine. Our observations, therefore, have failed to explain why in congestive heart failure there are no symptoms of histamine poisoning although the concentration of H Y S in the whole blood is much raised. The next step is to study the distribution of H Y S between the plasma and red cells.

3A *The concentration of H Y S in the plasma and red cells of heart failure and normal subjects*

The technique used for the removal of blood samples and for separation of red cells and plasma is of the greatest importance. At first a blood sample of 15 c.c. was taken either from an antecubital vein using little or no venous congestion of the arm or from the brachial artery. Either heparin or chlorazol fast pink was used to prevent clotting. The blood samples, so treated, were centrifuged promptly and the concentrations of H Y S in the plasma and in the red cell mass obtained by the centrifuging were determined separately. Samples of this red cell mass were found to contain 10% to

20% of plasma The percentage of plasma contaminating the red cell mass was determined for each blood sample by the hæmatocrit (9) The H Y S in the plasma and red cell mass was determined by Barsoum and Gaddum's method The concentration of H Y S in red cells uncontaminated by plasma was obtained by a simple calculation The results are seen in the following table

TABLE IV

The distribution of H Y S between plasma and red cells when an anticoagulant is used

Type of blood	Concentration of H Y S in γ per c c	
	Plasma	Red cells
Normal (venous)	0.03	0.16
Heart failure (venous)	0.02	0.25
Heart failure (venous) (very slight hæmolysis by spectroscopy)	0.06	1.00
Heart failure (venous) (very slight hæmolysis by spectroscopy)	0.05	0.80
Heart failure (venous)	0.025	1.20
Heart failure (venous)	0.02	1.00
(arterial)	0.025	0.90
Heart failure (venous)	0.03	0.25
(arterial)	0.03	0.25

Clearly the concentration of H Y S is greater in red cells than in plasma. It was observed, however, that very slight hæmolysis was associated with high concentrations of H Y S in the plasma. Then it was found that delay in centrifuging a blood sample increased the H Y S of its plasma. These two observations suggest that in shed blood the H Y S may leak out from the red cells and cause "in vitro" an increase in the concentration of H Y S in plasma even when no hæmolysis can be seen.

The use of anti-coagulants was thought, but was not proved, to be responsible for the leakage of H Y S from the red cells and therefore the following technique was adopted for all subsequent experiments. About 15 c.c. of blood is taken from an arm vein by a large bore needle lubricated with liquid paraffin and received directly into a centrifuge tube coated internally with paraffin wax. The blood is centrifuged at once and at full speed (5,000 r.p.m.) for a period of 3 minutes. Two-thirds of the plasma is then removed from the centrifuge tube for estimation of the H Y S. The red cells and the remaining plasma in the centrifuge tube are mixed carefully

and the concentration of the H Y S in the mixture is determined. A small portion of this mixture of red cells and plasma is treated with heparin to prevent clotting and the percentage of plasma in the mixture is determined by the hæmatocrit in order to calculate the concentration of H Y S in the red cells uncontaminated with plasma. The results obtained are shown in Table V.

TABLE V

The distribution of H Y S between plasma and red cells using the improved technique

Concentrations of H Y S in γ per c c			
Normal subjects		Congestive heart failure subjects	
Plasma	Red cells	Plasma	Red cells
0.006	0.13	0.006	
0.004	0.11	0.006	0.25
0.007		0.003	0.17
0.007	0.15	0.005	0.70
0.007	0.13	0.008	0.40
0.004	0.17	0.007	1.00
0.008	0.14	0.010	0.96
0.030 ?	0.25 ?	0.005	0.30
0.005	0.14	0.008	0.12
0.006	0.18	0.006	0.08
0.008	0.13	0.005	0.80
0.006	0.13	0.005	0.15
		0.007	0.42
		0.006	0.72

It is evident that the values of the H Y S in plasma obtained by the paraffined tube technique are much lower than those obtained when anti-coagulants are used. The H Y S concentration in the plasma of normal subjects is approximately the same as in subjects with congestive heart failure. The red cells usually contain much more H Y S in congestive heart failure cases than in healthy controls. The impression was gained that the concentrations of H Y S in the red cells which were within the normal limits occurred in the milder cases. Support for this view is found in a paper by Cerque (6) who found that the concentration of H Y S in whole blood was high in congestive heart failure and returned to normal on successful treatment.

3B *Evidence that the H Y S in the plasma of shed blood is also present in vivo and that the increased permeability of the capillaries in congestive heart failure is not due to the action of histamine*

It may be suggested that all the H Y S found in vitro in samples of plasma is due to leakage from the red blood cells after taking the blood samples. Estimation of the concentrations of H Y S in body fluids which are in diffusion equilibrium with the blood provides strong evidence that the H Y S is present in the plasma in vivo though in a low concentration.

In Table VI it is seen that oedema fluid and pleural fluid contain a concentration of H Y S which is of the same order as the H Y S of the

TABLE VI
The concentration of H Y S in plasma and plasma transudates

Type of Case	Concentration of H Y S in γ per c.c.			
	Red cells	Plasma	Oedema fluid	Pleural fluid
Heart failure	0.42	0.007	0.008	0.006
Heart failure	0.72	0.006	0.010	0.008
Heart failure	0.96	0.010	0.010	—
Heart failure	0.30	0.005	0.009	—
Heart failure	0.25	0.007	0.011	0.008
Nephritis	0.055	0.009	0.011	—
Nephritis	0.038	0.007	0.008	0.006
Nephritis	0.090	0.008	0.009	—
Nephritis	0.140	0.009	0.013	—
Nephritis	0.040	0.010	0.010	—
Pulmonary tuberculosis	0.080	0.006	—	0.008
Pleural effusion	0.12	0.008	—	0.010

plasma. As there is strong evidence that these two fluids are formed from plasma by ultrafiltration, the presence in them of H Y S at about the same concentration as in plasma suggests that the H Y S in the plasma is present in vivo as well as in vitro.

In congestive heart failure the concentrations of H Y S in both plasma and oedema fluid are within normal limits. Therefore both sides of the capillary blood vessels are in contact with fluids having a normal concentration of H Y S. It is unlikely therefore that the increased permeability of the capillary blood vessels in congestive heart failure is due to the abnormally high concentration of H Y S present in the whole blood of these cases.

30 *Evidence that H Y S and histamine when confined within the red cells do not show biological activity*

Two or three c c of human blood, whether laked or unlaked, injected intravenously into an anæsthetised cat or dog (ether or medinal) have but little effect on the blood pressure. This result is to be expected, for the amount of H Y S present in 3 c c of human blood, if all is in the form of active histamine, would be insufficient to produce an appreciable fall in the blood pressure when so injected.

It has been shown, however, that the concentration of H Y S in rabbits' blood is high. For this reason rabbits' red cells washed free from plasma and suspended in saline were used for the following experiment. A sample of rabbits' red cells was divided into two equal parts. One part was untreated and one was laked. It was observed many times that the intravenous injection of $\frac{1}{2}$ c c of unlaked rabbits' red cells had no effect on the blood pressure of the cat. Injection of an equal quantity of laked rabbits' red cells caused a marked fall in blood pressure.

It has been shown already (2) that the concentration of histamine in dogs' red blood corpuscles can be raised to a high level by the addition of histamine to the blood. The histamine-rich plasma was removed and the red cells washed several times with histamine-poor plasma. The red cells retained a high percentage of the histamine but on injection they had no effect on the blood pressure of an anæsthetised cat. An injection of a second sample of these histamine-rich red cells which was laked previous to the injection caused a marked fall in the blood pressure.

These observations indicate that histamine and H Y S from the red cells have no action on the blood pressure so long as they are confined within the red cells. When freed by laking the red cells they cause a fall in the blood pressure of the anæsthetised cat. Thus there is no difficulty in explaining the presence of high concentrations of H Y S in the whole blood of patients who are showing no physiological indication of such an excess.

CONCLUSIONS

A *The nature of the histamine yielding substances in blood*

It was shown by Barsoum and Gaddum that when blood is extracted by the method described in their paper, a substance appears in the extract which has many properties in common with histamine. The evidence that this substance in the extracts is actually histamine appears to be strong and is further supported by our observation that the histamine-like activity of the extracts is destroyed by a preparation containing histaminase. This paper concerns the nature of the mother substance in blood which on extraction by Barsoum and Gaddum's method yields a histamine-like body. The following observations show that H Y S has biological properties which bear a striking resemblance to those of histamine and that H Y S may be identical with histamine.

1 The histamine yielding substance (H Y S) in normal blood and blood from heart failure cases, as estimated by Barsoum's and Gaddum's method, is destroyed by a preparation containing histaminase

2 The H Y S is present in human liver and injections of watery extracts of liver produce a fall of blood pressure in anaesthetised dogs. The substance which produces this fall of blood pressure is mostly destroyed by a preparation containing histaminase

3 Rabbits' red cells contain a high concentration of H Y S and laked rabbits' blood, when injected intravenously, causes a fall of blood pressure of the anaesthetised dog, and when applied directly to the isolated guinea pig ileum causes it to contract. These histamine-like properties are destroyed by a preparation containing histaminase and destruction is associated with a decrease in the concentration of H Y S, as estimated by Barsoum and Gaddum's method

4 It is characteristic of histamine that the exposure of the isolated guinea pigs' ileum to high concentrations of histamine desensitises the ileum to a subsequent dose of histamine but does not desensitise it to other stimulants. It is found that the guinea pig ileum when desensitised to histamine is also desensitised to laked rabbits' blood, which blood fails to cause contraction of the desensitised ileum. Likewise the guinea pig ileum can be desensitised to histamine by the previous application of laked rabbits' blood. The laked rabbits' blood after treatment with a preparation containing histaminase loses its capacity to desensitise the guinea pigs' ileum to histamine and to laked rabbits' blood untreated with the preparation of histaminase

5 Equal doses of histamine and of H Y S (as estimated by Barsoum and Gaddum's method) cause equal contractions of the isolated guinea pig ileum and equal falls of blood pressure in anaesthetised dogs

B *The histamine yielding substance in the blood of congestive heart failure cases*

1 It was found that in congestive heart failure cases there is an increase in the concentration of H Y S in whole blood which is due exclusively to the increased concentration of H Y S in the red cells. H Y S when confined within the red cells fails, however, to produce its usual depressor action upon the blood pressure. Thus the absence of any measurable increase in H Y S in the plasma of heart failure cases seems to explain fully the absence of physiological or symptomatic indications of the excess of histamine in the whole blood of these cases

2 The concentrations of H Y S in plasma and in plasma transudates such as oedema fluids and pleural fluids are approximately equal. This suggests that the H Y S found in the plasma in vitro is present also in vivo

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3 The concentration of HYS in plasma and oedema fluid from congestive heart failure cases is within the normal limits This suggests that the presence of an excess of HYS in whole blood does not explain the increased permeability of the capillary bed in congestive heart failure

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OBSERVATIONS ON THE INCREASE IN THE CONCENTRATION
OF A HISTAMINE-LIKE SUBSTANCE IN HUMAN VENOUS BLOOD
DURING A PERIOD OF REACTIVE HYPERÆMIA

By G S BARSOUM and F H SMIRK

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LEWIS AND GRANT (4) presented strong evidence that reactive hyperæmia is due mainly to chemical substances which accumulate in the limb when the circulation of blood through the limb is obstructed. The degree of hyperæmia on release of the circulation was proportional to the duration of the circulatory arrest. Barsoum and Gaddum (2) using their method for the determination of the histamine equivalent of blood (1) found, in dogs, an increase above the normal in the histamine equivalent of whole blood taken from the veins of a limb which is in a state of reactive hyperæmia.

In Barsoum and Gaddum's method for estimating the histamine equivalent of blood an extract of the blood was prepared by chemical means. Strong evidence was advanced that the histamine-like substance found in the blood extracts is histamine. Barsoum and Smirk (3) have called the mother substance in untreated blood which on extraction yields a histamine-like body, histamine yielding substance (H Y S). A study of the properties of H Y S (3) led to the conclusion that "H Y S has biological properties which bear a striking resemblance to those of histamine. H Y S may be identical with histamine."

The distribution of H Y S between the plasma and red cells differs in man and dog. In the dog the concentration of H Y S is about the same in the plasma and red cells. In normal men the concentration of H Y S in the corpuscles lies between 0.05 and 0.20 γ * per c.c. and in the plasma between 0.002 and 0.010 γ per c.c.

Evidence advanced in the previous paper (3) indicates that the concentration of H Y S may be much increased in the red cells at a time when the concentration in the plasma is within normal limits. It has been shown that H Y S when confined within the red cells does not cause dilatation of the minute blood vessels. Therefore a rise of the concentration of H Y S in whole blood will explain reactive hyperæmia only if the H Y S of the plasma is increased.

* γ = 0.001 mg

For these reasons a study in man was made of the concentration of H Y S in the plasma and red cells of venous blood removed from an arm during a period of reactive hyperæmia

Results

The subjects of the experiments were normal men or male hospital patients suffering from surgical disabilities such as hydrocele or hernia. Blood was collected from the antecubital veins. The plasma and red cells were separated in the manner described in a previous paper (3) and the concentrations of H Y S were estimated by the method of Barsoum and Gaddum (1). Venous blood was removed from one of the arms to serve as a control and a sphygmomanometer cuff was then placed round the other arm. The sphygmomanometer cuff was inflated to above the systolic pressure, thus preventing a flow of blood through the arm. This period of vascular occlusion lasted 10 to 30 minutes. At the end of the period of occlusion a needle was inserted into an antecubital vein of the arm with the circulation obstructed. The circulation was released and 15 to 20 c c of blood was removed during the early stage of the reactive hyperæmia which followed the release of the pressure in the cuff. The following results were obtained —

TABLE I

The concentration of H Y S in venous blood from normal arms and arms in a state of reactive hyperæmia

Normal Concentration of H Y S in γ per c c		Duration of Circulatory arrest	Reactive hyperæmia Concentrated H Y S in γ per c c	
Plasma	Corpuscles		Plasma	Corpuscles
0.005	0.150	10 mins	0.020	0.150
0.012	0.120	10 "	0.025	0.120
0.006	0.130	10 "	0.011	0.135
0.005	0.110	10 "	0.009	0.120
0.003	0.200	15 "	0.008	0.250
0.005	0.139*	15 "	0.010	0.180*
0.006	0.180*	15 "	0.050	0.250*
0.008	0.125*	15 "	0.040	0.150*
0.005	0.140	30 "	0.020	0.200
0.009	0.150	30 "	0.060	0.250

* Values uncorrected by hematocrit for admixture with plasma

It has been shown already (3) that the biological properties of H Y S and histamine are similar. Equal amounts of H Y S and histamine cause approximately equal falls in the blood pressure of the anæsthetised dog (3). It is clear, therefore, that the observed increase in the concentration of H Y S in the plasma must favour the dilatation of the small blood vessels in the arm and must account in part for the phenomenon of reactive hyperæmia.

SUMMARY

During reactive hyperæmia of the human arm, following a period of complete obstruction to the circulation, there appears in the venous blood an increase in the concentration of a substance which has the biological properties of histamine. It is thought that the liberation of this histamine-like substance during circulatory arrest accounts at least in part for the hyperæmia.

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THE EFFECT OF CUTANEOUS BURNS ON THE BLOOD-HISTAMINE

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THE effects of extensive cutaneous burns have frequently been described and discussed. The patient commonly recovers from the initial shock and appears to be in good condition for many hours. Secondary shock is responsible for most of the deaths. Most authorities agree that the secondary shock is due to toxæmia, and a large number of theories have been put forward as to the nature of the toxin (2, 7, 9, 17 and 25).

When Dale and Laidlaw (6) studied histamine shock in cats, they drew attention to the similarities between this condition and the shock following mechanical trauma. They suggested that the absorption of histamine, or some similar substance, might be the cause of traumatic shock. Recent work on shock due to mechanical trauma has led to the conclusion that this is not due to the absorption of toxic substances (for references see O'Shaughnessy and Slome (16)). The shock due to burns is, however, a different condition (Simonart (21)), and the conclusion that it is due to toxæmia is not affected by the work on mechanical trauma.

Evidence of the release of a toxin as a result of burns was obtained by Vogt (24), who found that if a burned area of skin was transferred from one guinea-pig to another, the first survived and the second died. If the circulation and the peritoneum of one guinea-pig was united in a preliminary operation to the circulation and the peritoneum of a second guinea-pig, burning the skin of one animal killed both. Experiments in which rats or mice were similarly united gave similar results. Vaccarezza (23) reached similar conclusions as a result of experiments on chloralosed dogs. If the skin of one leg was burned with a blow-pipe the dog died in 6-10 hours. If the femoral artery was tied, or if the skin was excised, the dog survived. If the femoral artery and vein were united to the carotid artery and jugular vein of a second dog, this second dog died, and the first survived. Fender (9) working with Guptill failed to confirm some of these results of Vaccarezza.

Direct evidence that cutaneous burns are associated with an increased absorption of histamine into the circulation was obtained by Harris (10), who showed that cutaneous burns led to the disappearance of extractable histamine-activity from the skins of anaesthetised cats. The burn caused

the extravasation of fluid, and the histamine appeared to be absorbed with this fluid. In these experiments a large proportion of the histamine activity was absorbed from the skin in the course of 60 minutes. Since secondary shock usually develops many hours after the burn it is unlikely that it is due to the phenomenon observed by Harris. This possibility cannot, however, be definitely excluded, since it is possible that the rate of absorption in an anesthetized cat is quite different from that in man.

Nevertheless the similarity between burn shock and histamine shock is sufficient to suggest that the two conditions may have something in common. In both conditions the blood-pressure is low, and the pulse is weak and rapid. The concentration of haemoglobin, or cells, in the blood is high (1, 6, 14, 21, 22), the blood-chloride is low (20, 21, 22), and the blood-non-protein-nitrogen is high (8, 12, 19), there is a secretion of adrenaline (4, 5, 11), and gastric juice (13, 18). Both conditions appear to be relieved by the injection of extracts of the suprarenal cortex (15, 26).

In view of these facts it was decided to estimate the blood-histamine of burned patients. About 10 c.c. of blood was collected for each estimation from the cubital vein at about 9 a.m. The blood was immediately mixed with 15 c.c. of trichloroacetic acid (10 p.c.) and the estimation was then carried out by the method already described (Barsoum and Gaddum (3)). The patients were all under the care of Professor Arnold Henry in Kasr el Ain Hospital, Cairo. We are grateful to him for permission to use this material, and for helpful discussion. The burns were all treated with tannic acid.

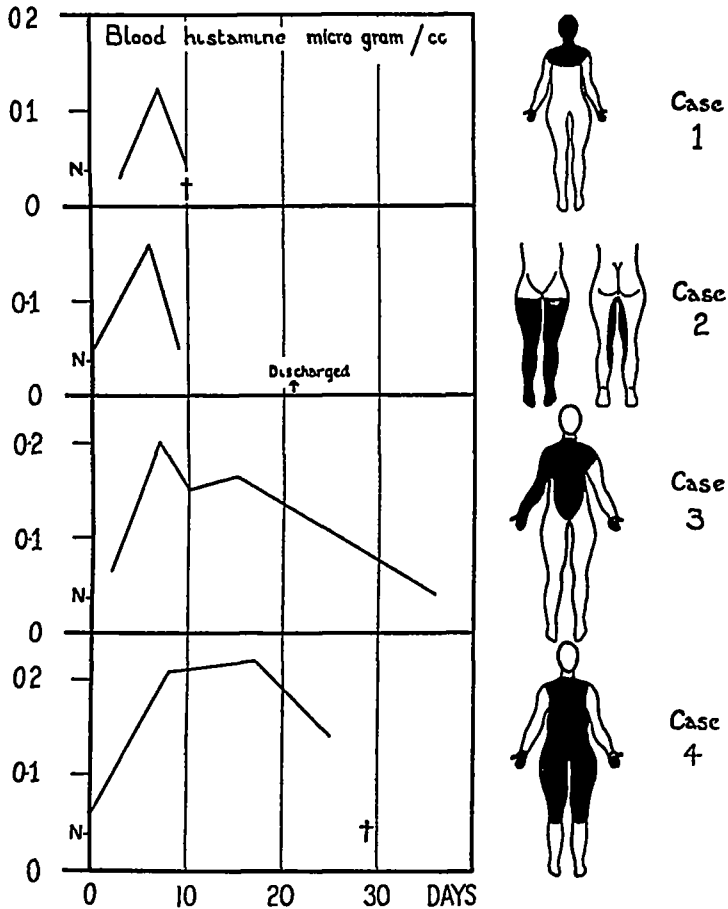
Normal blood-histamine

The blood histamine of five control subjects was estimated. The values obtained were 0.027, 0.03, 0.03, 0.04 and 0.05 microgram per c.c. The mean of these figures is 0.035 microgram per c.c. Three of these subjects were apparently normal and the others were patients in the hospital with minor complaints. As the figures given above were obtained from only five subjects, their average does not represent a reliable estimate of the normal blood-histamine. This fact does not invalidate the conclusions reached below, since these conclusions are based on a comparison of values obtained at different times with blood from the same patient.

Blood-histamine in burned patients

Case 1 M.A., a woman of 70, was admitted to hospital with second and third degree burns over the face and the front of the chest, and on both hands. She was treated with tannic acid. Pulse rate on admission 110 per minute. This fell to 80 after 48 hours and never again rose above 100. She developed broncho-pneumonia, and died on the tenth day after the burn. No post-mortem. The results of the estimates of blood histamine in this and other illustrative cases are shown in Fig. 1.

Case 2 S, a woman of 22 with second and third degree burns on the front of the legs was treated with tannic acid. Her recovery was uneventful and she was discharged from hospital 12 days after the burn.



Estimates of the blood histamine-equivalent at different periods after burning. N—represents the average value for five normal persons. The blackened areas in the figures to the right show the extent of second and third degree burns.

Case 3 W A, a woman of 25 with second and third degree burns over the whole front of the trunk from the neck to the symphysis pubis, and on the front of one arm and both hands was treated with tannic acid. On admission her pulse rate was 120 per minute. It fell gradually to 82 on the fourth day, and then was about constant between 80 and 90. Her temperature was about normal until the 12th day, when the burn became infected and her temperature rose to 38.4°C. A week later the infection

subsided and her temperature became normal. Her general condition improved slowly, and eventually she recovered.

Case 4 N, a woman of 25 with second and third degree burns over the whole front of the trunk and legs from the neck to the knees, and on both hands was treated with tannic acid. About 3 weeks after the burn the skin became infected. The infection progressed and she died a week later. No post-mortem.

Case 5 A boy of 9 who was burned practically all over and died in the first 24 hours. His blood histamine was 0.082 mg per c.c. and thus above the normal range. No post-mortem.

Case 6 H.M., a woman whose age was given as 160 was admitted with burns more extensive than those of *Case 4*. A sample of blood taken an hour after admission contained a normal quantity of histamine (0.04 microgram per c.c.). She died 16 hours after the burn. No post-mortem. This patient did not survive until the time at which the blood-histamine rose in other patients.

Other cases Samples were taken from three other burned patients, and the results were in essential agreement with those given above. The blood-histamine rose after admission to hospital, and was high about one week after the burn.

DISCUSSION

These results show that extensive cutaneous burns are followed by a rise in the histamine-equivalent of blood extracts, as estimated by the method used. After large burns the histamine-equivalent rose to at least four times its normal level, and was maintained at high values for many days. Smaller burns caused smaller effects, and there appeared to be a direct relation between the area of the burn and the magnitude and duration of the rise in histamine-equivalent.

Certain of the extracts were subjected to additional tests of the nature of their active principle. All these tests pointed to the conclusion that it was histamine. When extracts showing a high histamine-equivalent were assayed both on the guinea-pigs ileum and the hens rectal caecum, the two assays agreed quantitatively with one another. When these tests were otherwise complete, a large excess of histamine was added to the bath containing the rectal caecum. This had the effect of rendering the muscle insensitive to further small doses of histamine and insensitive to the extracts, but it was still normally sensitive to other stimulating substances such as acetylcholine or barium. These observations provide strong evidence that the active substance was histamine itself.

The relation of this rise in blood histamine to secondary shock is uncertain. There was no clear evidence of any correlation between the blood histamine and the clinical condition of the patient. Neither the pulse-rate, nor the temperature, was significantly altered during the rise in blood-histamine. No systematic observations of the blood-pressure were made. The time at which the rise in blood histamine occurred was rather later than that usually given for the onset of secondary shock, but corresponded with the time at which secondary shock occurred among these Egyptian patients.

It is reasonable to suppose that the reason why the observed increase of blood-histamine did not produce shock in the cases studied, is that it was not large enough, and that if the burns had been more severe the blood histamine would have increased sufficiently to cause secondary shock. Before accepting this theory, however, it is clearly desirable to know the value of the blood-histamine during histamine-shock in man.

The mechanism of the rise in blood-histamine is obscure. It is doubtful whether the damaged skin could produce enough histamine to maintain a high concentration of this substance in the blood over a period of many days. It is possible that the rise in blood histamine is secondary to pathological changes in organs such as the liver and the kidneys. These changes might act either by constantly liberating histamine, or by damaging the mechanism by which histamine is normally removed from the blood.

SUMMARY

Extensive cutaneous burns cause in man a large rise of blood-histamine at about the time when secondary shock is liable to develop.

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	18/3/36	143 90	22*	2/4/36	130 70	22*
4	11/6/36	140 86	9.7	23/6/36	114 72	12.5
5	29/4/36	154 94	12.0	10/7/36	125 85	10.4

* Estimated by the histamine method

The results are shown in Table I from which it may be seen that for a given subject the circulation times were essentially similar during and after the phase of hypertension. It is unlikely therefore that the raised pressure in acute nephritis is due to increased cardiac output, it is presumably due to increase in the resistance offered by the peripheral vessels to the flow of blood. It is shown in Table II that the blood viscosity is usually lowered during the phase of hypertension, and we may therefore, by exclusion, attribute the rise in arterial pressure to peripheral vasoconstriction.

The nature of the agent producing vasoconstriction in acute nephritis

In a recent paper (12) a method was described of testing if in hypertension the abnormal vasoconstriction arises through the action of the vasomotor nerves. If it does arise in this way then complete inhibition of vasomotor nervous impulses supplying a given territory should result in a greater bloodflow through this territory in the subject with hypertension.

than in the subject without, for the abnormal factor narrowing the vessels would thus be removed and, the vessels being in the same state in the two instances, bloodflow should be approximately proportional to blood pressure. The methods at present available enable us to carry out such an experiment only on the skin of the hand. In the previous paper (12) it was shown that, for comparative purposes, a reliable index of the bloodflow through the skin of the hand may be obtained by measuring its heat elimination by Stewart's method, and that vasomotor nervous tone is completely removed from this structure by abruptly raising body temperature. The "maximum rate of heat elimination" from the hand obtained in response to raised body temperature thus represents, for comparative purposes, the bloodflow through the skin of the hand from whose vessels vasomotor tone has been removed. This rate has been measured in the 6 cases of acute nephritis by the technique fully described previously (12) and which is briefly as follows.

One hand of the subject is immersed in a Stewart's calorimeter containing 3 litres of water at 30.5°C. The calorimeter is stirred at a constant rate and its temperature read at minute intervals from a mercury thermometer graduated in 1/100°C. The other arm is immersed in stirred water at 45°C, a procedure which, after a latent period of a few minutes, increases the rate of rise of calorimeter temperature to a maximum value at about which it remains till the experiment is terminated at a calorimeter temperature of 32°. After removing the hand the rate of cooling of the calorimeter is determined. The maximum rate of heat elimination (H) in calories per min. is then calculated as follows:

$$H = (V + E) \times (R + C)$$

where V is the water content and E the water equivalent of the calorimeter (in c.c.), R is the maximum rate of rise of calorimeter temperature while the hand is immersed and C the rate of cooling of the calorimeter after removing the hand (in °C per min.). The blood pressure and mouth temperature are measured at the beginning and end of the experiment, and the hand volume is measured by water displacement at the end of the experiment. After these measurements have been made, 20 c.c. of blood are withdrawn with minimum congestion from a forearm vein into 0.2 c.c. saturated potassium oxalate to prevent coagulation, and the blood viscosity determined by the rapid velocity method of Whittaker and Winton (16) in the way described previously (12).

These measurements were made repeatedly on the 6 cases and the results are summarised in Table II. In this Table the values for systolic and diastolic blood pressure were those recorded at the end of the determination of heat elimination, the values at the beginning of the observation were usually a few, but less than 10 mm Hg higher. The values for maximum heat elimination represent the maximum rate of heat elimination over the range of calorimeter temperature 31° to 32°, they are thus strictly comparable

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- (13) HENRY (Unpublished data)
- (14) LOCKE (Quoted by Wilson, 1929) Boston Med Surg J , 1902, 147, 480
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OBSERVATIONS ON THE MECHANISM OF ARTERIAL HYPERTENSION IN ACUTE NEPHRITIS

By G W PICKERING *

(From the Department of Clinical Research, University College Hospital
Medical School)

THE transient forms of human hypertension have in the past attracted less attention than have the persistent varieties, no doubt because they are less common, and because the number and complexity of the observations that can be made is limited by time. Nevertheless they offer considerable technical advantages for study, for a comparison may be made between data obtained in a single individual with and without hypertension, the factor of individual variation being thereby excluded.

The present paper records observations made on six patients with acute nephritis, in five the disease followed acute infection of the throat, in one (Case 4) it was associated with glandular fever. Brief clinical summaries of these patients are appended. The methods used in this analysis have nearly all been described in a previous paper (12).

The evidence for peripheral vaso-constriction

The cardiac output Theoretically, raised arterial pressure in acute nephritis might be due either to an increase in cardiac output or to an increase in the resistance offered by the systemic vessels to the flow of blood. The only estimate of cardiac output in acute nephritis seems to be one by Hayasaka (6) using the Fick principle and the triple extrapolation method, he found in one case that the cardiac output was 3,492 c.c. per min. when the systolic arterial pressure was 170 mm. Hg and 3,166 c.c. when the systolic pressure had fallen to 110 mm. Hg.

In view of the theoretical objections that have been raised to all methods of determining cardiac output in man it seemed more satisfactory to determine the linear velocity of bloodflow between a large vein and the systemic capillaries by the method largely worked out by Blumgart and Weiss and their co-workers (3, 15), for such determinations repeated in a single individual should reflect any significant alterations in cardiac output.

* Work undertaken on behalf of the Medical Research Council

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The results are shown in Table I from which it may be seen that for a given subject the circulation times were essentially similar during and after the phase of hypertension. It is unlikely therefore that the raised pressure in acute nephritis is due to increased cardiac output, it is presumably due to increase in the resistance offered by the peripheral vessels to the flow of blood. It is shown in Table II that the blood viscosity is usually lowered during the phase of hypertension, and we may therefore, by exclusion, attribute the rise in arterial pressure to peripheral vasoconstriction.

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One hand of the subject is immersed in a Stewart's calorimeter containing 3 litres of water at 30.5°C. The calorimeter is stirred at a constant rate and its temperature read at minute intervals from a mercury thermometer graduated in 1/100°C. The other arm is immersed in stirred water at 45°C, a procedure which, after a latent period of a few minutes, increases the rate of rise of calorimeter temperature to a maximum value at about which it remains till the experiment is terminated at a calorimeter temperature of 32°. After removing the hand the rate of cooling of the calorimeter is determined. The maximum rate of heat elimination (H) in calories per min. is then calculated as follows:

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in each subject, to make the values comparable in different subjects they have been expressed in the next column as calories per min per c c hand. The other features of the table require no further explanation.

TABLE II

Shows chiefly the maximum rate of heat elimination from the hand over the range of calorimeter temperature 31-32°C, in six cases of acute nephritis during and after the phase of hypertension

Case	Age	Sex	Date	Blood pressure mm Hg		Max heat elimination		Blood		Mouth temp		Oedema
				S	D	Cals per min	Cals per min per c c hand	Viscosity	Hb %	Beg	End	
1	24	M	16/3/36	166	94	467	1.24	—	86	36.7	37.4	Slight
			17/3/36	162	98	515	1.36	3.7	86	36.7	37.2	Slight
			21/3/36	140	78	445	1.17	—	90	36.7	37.0	Trace
			30/3/36	124	70	386	1.00	—	101	36.2	36.7	None
			30/3/36	126	68	400	1.04	—	101	36.7	37.1	None
			1/5/36	136	86	415	1.08	4.1	90	—	36.8	None
2	33	F	24/7/35	146	112	279	1.15	—	—	—	37.9	None
			24/7/35	135	95	260*	1.04	—	—	—	38.0	None
			5/8/35	118	78	233	0.93	—	—	—	37.9	None
			27/8/35	122	82	217	0.87	—	—	—	37.7	None
3	39	F	11/10/35	214	116	388	1.21	3.75	68	—	38.0	Slight
			12/10/35	208	114	388†	1.21	—	—	—	37.8	Slight
			15/10/35	208	114	396	1.23	—	—	—	38.0	Slight
			4/11/35	140	82	296	0.93	—	78	—	37.8	None
			9/11/35	152	86	295	0.93	4.15	82	—	37.8	None
4	28	F	10/6/36	146	100	448	1.49	4.15	78	38.0	38.3	None
			11/6/36	145	96	422	1.41	—	—	37.3	37.9	None
			24/6/36	124	85	362	1.21	3.8	78	37.3	37.7	None
			24/6/36	122	86	346	1.15	—	—	37.1	37.6	None
5	30	F	29/4/36	154	95	467	1.41	—	—	—	37.4	Slight
			30/4/36	155	96	489	1.44	2.6	70	—	37.2	Slight
			10/6/36	128	84	460	1.40	4.3	82	37.2	37.7	None
			10/7/36	130	76	458	1.39	3.7	82	37.2	37.8	None
6	8	M	29/8/35	156	110	288	1.38	—	73	—	37.8	Slight
			13/9/35	98	76	295	1.40	—	88	—	37.5	None
			18/9/35	80	60	276	1.31	—	89	—	37.4	None

* Determined in response to raising body temperature after previous anæsthetisation of the ulnar nerve at the elbow.

† Determined in response to raising body temperature after previous anæsthetisation of the ulnar nerve at the elbow and the median at the wrist.

It was mentioned in the previous paper (12) that in a single subject the maximum heat elimination varies by less than 5% on different occasions, provided that the blood pressure remains constant. From Table II it may be seen that the same is generally true in acute nephritis. It is unlikely therefore that alterations in maximum heat elimination of much more than 5% are due to chance errors.

During the phase of hypertension the maximum heat elimination from the hand was not increased by previous anæsthetisation with novocaine of the ulnar nerve at the elbow in Case 2, or by anæsthetisation of this nerve and of the median at the wrist in Case 3. We may conclude, therefore, that in acute nephritis with hypertension, as in normal subjects and subjects with persistent hypertension (12), raising body temperature in the way described virtually removes the influence of the vasomotor nerves from the skin of the hand.

In Cases 1 to 4 the maximum heat elimination showed variations considerably greater than the range of chance error and in the same direction as the variations in arterial pressure. Alterations in the maximum heat elimination can be produced by alterations in blood temperature and by alterations in blood viscosity as well as by alterations in the arterial pressure and in the tone of the vessels of the hand. Of these factors the temperature of the blood may be dismissed with the remark that the variations in blood temperature, as indicated by mouth temperature, were too small to produce any definite variation in heat elimination except in Case 4, this patient was febrile during the first observation and the observation will therefore be eliminated from subsequent discussion. The fall in blood viscosity during the initial stages of Cases 1 and 3 may have contributed to the increase in the maximum heat elimination from the hand but cannot have been a chief factor, for in each case the fall in viscosity was of the order of 10%, whereas the rise in heat elimination was of the order of 30%. In Case 4, moreover, the blood viscosity was slightly increased during the phase of hypertension, in Case 2 the viscosity was not measured. It is concluded that in these cases the chief factor responsible for the changes in heat elimination was the arterial pressure.

In a previous paper (12, p. 224), an observation was described on a patient with a large arteriovenous fistula of the femoral vessels in whom the blood pressure could be raised at will by compressing digitally the artery proximal to the fistula, this observation showed the order of change of maximum heat elimination that is produced by a given change in arterial pressure, all other known factors, including the tone of the hand vessels, remaining constant. The relationships between maximum heat elimination and diastolic arterial pressure observed in this patient and in Cases 1 to 4 of the present paper are shown in Fig. 1, the diastolic pressure has been chosen as being a closer approximation to mean arterial pressure than is the systolic value. It may be seen from this figure that a given rise of arterial pressure produced increases of heat elimination of the same order in the patients with acute nephritis as in the patient with arteriovenous fistula. In these cases of acute nephritis, therefore, the difference in the rates of maximum heat elimination observed in the different stages of the disease are such as would be expected from the observed changes of arterial pressure if, under the circumstances of the experiments, the tone of the vessels of the hand were the same when the blood pressure was high as when it was low. Thus we may say that in these four cases of acute nephritis during the phase

of hypertension no abnormal vasoconstriction could be demonstrated in the hand after completely inhibiting vasomotor nervous impulses to it. This result is quite different from that previously obtained in chronic nephritis and other forms of persistent hypertension in which raised blood pressure was found to be unassociated with any increase in the rate of maximum heat elimination from the hand (12). It is incompatible with the possibility of hypertension being due to vasoconstriction of chemical origin in these 4 cases, except in the unlikely event of the chemical agent being one that has no action on the skin vessels of the hand. It is compatible with

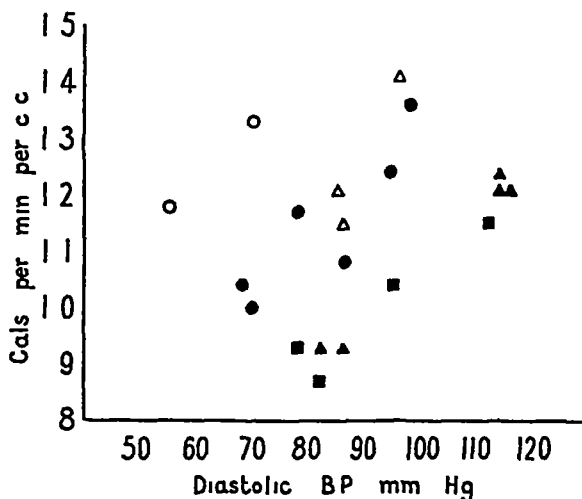


Fig 1 Shows the relationship between the maximum rate of heat elimination from the hand (in cals per min per c c hand) and diastolic arterial pressure (in mm Hg) in the case of arteriovenous aneurysm (open circles), and Cases 1 (solid circles), 2 (solid squares), 3 (solid triangles), and 4 (open triangles) of the present series

the possibility that hypertension is due to increased cardiac output, an explanation which has, however, been shown to be improbable in the previous section. The only explanation with which the observations here presented are in simple agreement is that in these four cases of acute nephritis the hypertension was due to vasoconstriction of vasomotor nervous origin.

In Cases 5 and 6 the increases in maximum heat elimination during the phase of hypertension were small and were within the range of chance error. It is possible that in these two cases the hypertension was due to vasoconstriction of chemical origin, the vessels of the hand remaining abnormally constricted after loss of vasomotor nervous tone during the hypertensive phase, but other explanations cannot be excluded. Thus it has been shown previously (12) that Stewart's method probably under-estimates large as compared with small bloodflows, in these two cases the maximum rate of heat elimination was large during the phase of normal blood pressure, and it is possible that in them an increased bloodflow through the hand during

the phase of hypertension was not reflected by any significant increase in heat elimination. Clinically there was no clear difference between Cases 5 and 6 and Cases 1 to 4. Prinzmetal and Wilson (13) found that novocaine injection of the appropriate sympathetic ganglia produced an apparently normal increase in forearm bloodflow in one case of acute nephritis.

DISCUSSION

The chief point of interest that emerges from this work is the suggestion that in some, and probably most, cases of acute nephritis hypertension is due to vasoconstriction of vasomotor nervous origin. Although this suggestion is out of harmony with Volhard's well-known theory of the mechanism of pale hypertension (14), yet there is no definite evidence standing in its way, the claim by Bohn (4) that in acute nephritis and other forms of so-called "pale" hypertension a pressor substance can be obtained from the plasma by alcoholic extraction has not been confirmed in the case of acute nephritis by Page (11) or in other forms of hypertension by numerous workers. Vasoconstriction of nervous origin might conceivably arise in one of two ways, either by the presence in the blood of some centrally acting pressor substance or by a reflex mechanism. Of these two possibilities the latter is by far the more probable, and it is natural to look for the origin of such a reflex in the organ which alone shows constant anatomical abnormalities in acute nephritis, namely, the kidney. Although no such reflex has yet been demonstrated, it may be presumed to exist from the work of Arnott and Kellar* (1) who have shown that in the rabbit the hypertension which ordinarily accompanies oxalate nephritis does not appear if the kidneys are previously denervated.

The conception of hypertension originating reflexly from the kidney in acute nephritis is not new, but does not conform with recently expressed opinion. In 1917 Nonnenbruch (10) showed that in many cases of the acute nephritis of war time, oedema and hypertension preceded by several days the appearance of albumen and blood in the urine. The early appearance of hypertension has been confirmed repeatedly for the acute nephritis following scarlatina and other acute infections by Kylin (8), Koch (7) and Bayart (2). For this reason the majority of recent writers have abandoned the view that the hypertension of acute nephritis is secondary to the renal lesion, and suppose that the rise in blood pressure is an expression of some primary disturbance in the vascular system, the exact nature of which is uncertain. The question has been recently reopened by the work of Masugi (9). This author has prepared a nephrotoxic serum by injecting ducks with emulsions of rabbit's kidney, injected into rabbits this serum produces an acute glomerulonephritis histologically identical with the human disease, and likewise characterised by hypertension, nitrogen retention and the appearance in the urine of albumen, blood and casts, as in man, so in the rabbit, the

* Drs. Arnott and Kellar tell me that they have recently found that the hypertension ordinarily accompanying acute nephritis produced in the rabbit by nephrotoxic serum similarly fails to appear after renal denervation.

rise of blood pressure precedes the albuminuria. The method of producing the disease tempts one to suppose that in the rabbit the hypertension results from the renal lesion, but it is to be borne in mind that as yet no adequate lesion of the kidney has been demonstrated at the time of onset of hypertension.

The methods used in this and the preceding paper lead to different conceptions of the mechanism of hypertension in acute as opposed to chronic nephritis, current conceptions of the mechanism of oedema formation in the acute and subacute stages of the disease similarly differ. In the previous paper (12) it was shown that the maximum rates of heat elimination from the hand are no greater in patients with chronic nephritic, essential and

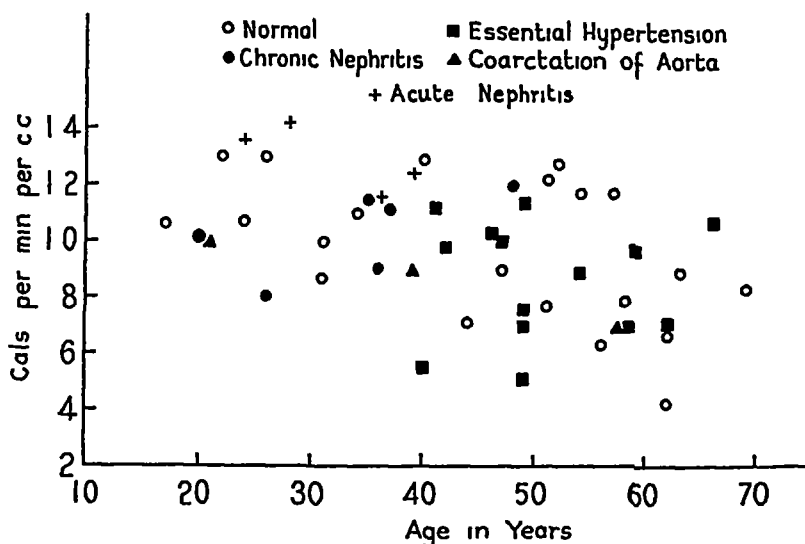


Fig 2 Shows the maximum rate of heat elimination (in cals per min per cc hand) obtained in subjects with normal and raised blood pressures

malignant hypertension than in normal subjects of similar age, and it was tentatively concluded that in these conditions hypertension is due to vasoconstriction of non-nervous, and presumably chemical, origin, similar conclusions were drawn by Prinzmetal and Wilson (13). If we are right in believing that in acute nephritis the hypertension is of vasomotor nervous origin, whereas in chronic nephritis and other forms of persistent hypertension it is not, then it is evident, from the argument developed in this and the preceding paper, that the difference ought to be apparent from a comparison of the maximum rates of heat elimination from the hand obtained in the several conditions. Fig 2 is a reproduction of Fig 3 of a previous paper (12) to which have been added data since obtained for one case of chronic nephritis and for Cases 1 to 4 of the present series. It may be seen from this figure that in these patients with acute nephritis the maximum rates of heat elimination are at or above the upper normal limit, whereas in the patients with chronic nephritis and other forms of persistent hypertension the maximum rates of heat elimination are

indiscriminately scattered within the normal limits When it is recalled that the degree of hypertension exhibited by the patients with acute nephritis was small in comparison with that ruling in the other conditions, the probability of an essentially different mechanism is evident

SUMMARY

1 Raised arterial pressure in acute nephritis probably results from vasoconstriction because —

- (a) In three cases the circulation time, as estimated by the decholin method, was essentially the same when the blood pressure was high and when it was normal
- (b) The blood viscosity was slightly decreased in three and slightly increased in one patient during the phase of hypertension

2 In four out of six cases of acute nephritis estimations of bloodflow showed that during the phase of hypertension no abnormal vasoconstriction was present in the hand from which vasomotor nervous tone had been completely removed

3 Hypertension seems to be due to vasoconstriction which is of essentially different origin in acute and chronic nephritis, in the former it is probably of nervous origin in most cases, in the latter it is probably not

CASE REPORTS

Case 1 E.L., a man of 24 years, suffered from sore throat with enlarged cervical glands from 5/3/36 to 9/3/36 On 14/3/36 he noticed swelling of his face and ankles and on the following evening his urine was dark in colour He was admitted to hospital on 16/3/36 on which day he did not urinate till 4 p.m. when he voided 600 c.c. of dark urine containing 0.2% albumen, macroscopic blood, and numerous red cells and granular and blood casts in the centrifuged specimen He had a slight generalised oedema, his systolic and diastolic blood pressures were 168 and 102 mm Hg, and the blood urea 70 mg per 100 c.c. The blood pressure fell to 130/80 on 19/3/36 and the oedema disappeared by 23/3/36 On discharge from hospital on 4/5/36 the blood pressure was 125/70, the blood urea was 38 mg %, and there was no oedema but the urine still contained a trace of albumen and a slight excess of red blood cells On 7/9/36 the blood pressure was 132/82 and the urine contained the faintest trace of albumen and a slight excess of red cells

Case 2 F.M., a married nulliparous woman of 33, noticed swelling of her legs and face on 11/7/35, three weeks previously she had a sore throat lasting about two weeks On 17/7/35 she went to bed and by the following day her oedema had disappeared, but she complained of headache She was admitted to hospital on 20/7/35 and when examined on 23/7/35 she had no oedema, the systolic and diastolic arterial pressures were respectively 160 and 100 mm. Hg and the urine contained albumen macroscopic blood, and casts The blood pressure fell to normal in ten days On discharge on 11/9/35, the urine contained a faint trace of albumen and a slight excess of red cells On 10/9/36, the blood pressure was 118/78 and the urine was normal

Case 3 H.E., a nulliparous housewife of 39 years had two attacks of tonsillitis with pyrexia and cervical adenitis in August, 1935 A week after the last attack her face and hands swelled, and she suffered from epigastric pain and vomiting and severe headaches On 8/10/35 she had a severe headache followed by two epileptiform convulsions and unconsciousness She was admitted to hospital on 9/10/35 in a drowsy condition no abnormal physical signs were found in the nervous system There was slight generalised oedema the systolic and diastolic blood pressures were respectively 160 and 88 mm Hg, the blood urea was 63 mg % and the urine contained much albumen, and many red blood cells, and blood and cellular casts A venesection of 250 c.c. did not alter her condition On the following day the blood urea had fallen to 34 mg % and she became alert, there were no further cerebral disturbances The blood pressure gradually rose to 205/115 on 14/10/35 and then fell gradually to reach 138/90 on 8/11/35 at about which

value it remained thereafter. The oedema disappeared by 23/10/35. On 13/11/35 the maximum concentration of urea in the urea concentration test was 1.8%. On discharge, 11/1/36, the urine still contained albumen and red blood corpuscles.

Case 4 K L, a nurse aged 28 years, was admitted to hospital on 7/6/36 complaining that two weeks previously she had felt tired and "run down", three days later her eyelids swelled and two days later her cervical glands enlarged and she noticed white patches on her tonsils. On admission she was found to have follicular tonsillitis with enlarged cervical and axillary glands, although there was no oedema the systolic and diastolic arterial pressures were 150 and 110 mm Hg respectively, and the urine contained a trace of albumen with numerous red cells and granular casts in the centrifuged specimen, the blood urea was 27 mg %. A blood count on 12/6/36 showed 10,700 white cells per c mm of which 10% were polymorphonuclear, 78% lymphocytes and 9% monocytes, the serum agglutinated sheep's red blood cells in a dilution of 1 in 512, confirming the clinical diagnosis of glandular fever. An Addis count on the urine on 12/6/36 showed an excretion rate of 2,500,000 red cells and 140,000 casts per 12 hours confirming the diagnosis of acute nephritis. On discharge 25/6/36, the blood pressure was 115/75, the urine contained only the faintest trace of albumen and no cells and the glands were of normal size.

Case 5 F T, a housewife of 30, who had had two normal pregnancies, the last six years ago, suffered from a sore throat on 13/4/36 lasting two days. On 21/4/36 her eyelids swelled, followed on 24/4/36 by swelling of the feet. On admission on 29/4/36, she had slight generalised oedema, the systolic and diastolic arterial pressures were respectively 150 and 95 mm Hg and the urine contained much albumen and many red cells and blood, epithelial and granular casts. The oedema disappeared by 18/5/36, but the blood pressure remained elevated till the beginning of June when it had fallen to 124/85. On discharge, 10/7/36, the urine still contained a trace of albumen and a slight excess of red cells. On 7/9/36 the blood pressure was 132/82, the urine contained the faintest trace of albumen and a slight excess of red cells.

Case 6 L H, a boy of 8½ years, had a sore throat lasting one day on 15/8/35. A week later he lost his appetite and suffered from headache and his urine was scanty and dark. On 26/8/35 his eyelids and face became swollen. Admitted to hospital on 28/8/35 he was found to have slight generalised oedema, the systolic and diastolic pressures were respectively 174 and 110 mm Hg, and the urine contained much albumen and many red cells and granular and epithelial casts, the blood urea was 70 mg % on 30/8/35. The systolic blood pressure remained between 140 and 150 mm Hg for several days and then fell, reaching 90 mm Hg on 7/9/35. The blood urea was 49 mm Hg on 9/10/35. On discharge on 12/11/35 the urine still contained a trace of albumen and a slight excess of red cells, the urea concentration test was up to 2.5% urea. On 7/9/36 the blood pressure was 98/68, and the urine was normal.

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EXPERIMENTS RELATING TO CUTANEOUS HYPERALGESIA AND ITS SPREAD THROUGH SOMATIC NERVES *

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THE experiments described in this paper were begun in the hope of more clearly understanding hyperalgesia of the skin. The skin of healthy subjects submitted to one of several forms of deliberate injury becomes tender, and skin so injured was investigated by Hess and myself (6) a few years ago. During the course of this and other work upon cutaneous reactions, I often noticed that hyperalgesia is not confined to the area exhibiting obvious vascular signs of inflammation, but spreads widely beyond it, the same thing was noticed in instances of local infections of the skin, and I made particular mental note of widespread hyperalgesia around a point of faradic stimulation of the skin. This diffuse hyperalgesia interested me especially, and preliminary experiments undertaken two years ago soon convinced me that it could be studied successfully, and that its investigation might possibly throw light on the long disputed origin of referred tenderness.

Professor R. Hussey, of Yale University, became interested in these observations while visiting my laboratory this year, and a large number of the experiments done on my own skin were repeated on his. Thus it was my good fortune to have at my disposal the independent observations of a trained worker to whom I here gratefully acknowledge this help. The third subject of experimentation has been my laboratory assistant, Mr. A. J. Honour, upon the accuracy of whose observations I have long known I can rely.

Where it is not otherwise specifically indicated, it is to be understood that the experiments described have been carried out upon these three subjects with results that have been in harmony.

PART I HYPERALGESIA FROM INJURIES OF THE SKIN

Hyperalgesia following faradisation of the skin

When a strong faradic current is applied to the surface of the forearm, it is frequently noticed that an area around the point of stimulation subsequently becomes sore, in the sense that it is sensitive to light friction. The development of soreness varies much in degree and in extent in different individuals, with different strengths of current and with the duration of stimulation. To obtain an adequate area of soreness, it is always necessary to use the faradic current at a strength giving considerable pain and raising a distinct area of goose skin for several centimetres around the twin points of the stimulating electrodes. The current should be continued at this almost unbearable intensity for a period of about 5 min. Even so the effect from subject to subject is inconstant. In a few subjects no noticeable soreness of the skin develops, in most subjects it is identified without difficulty, in a number it is conspicuous and widespread, naturally, it is in the last that the phenomenon can be investigated most successfully. The following example is chosen to illustrate the effects as these are witnessed in such a subject. Stimulation was applied for 5 minutes to a chosen point of the skin of the lower part of the front of the forearm. The stimulation caused prominent local goose skin, which was maintained to the end of the stimulation, by which time a wide area of surrounding skin was flushed. At the end of stimulation (5th min) little or no soreness of the surrounding skin could be detected, on the contrary it seemed a little numb to light friction. At the 6th min, however, this gave place to soreness, sufficiently well defined to be outlined on the skin (Fig 1, area marked "6 min"), the faradic current had injured the skin, which was showing a definite small wheal (*w*). The soreness increased in intensity and spread farther up and down the arm, increase in the area being mapped out at the 9th, 11th and 16th minutes. A curious tongue of soreness was noticed extending up the arm and covering three chief superficial veins, the courses of which are indicated by dotted lines in Fig 1. The total area extended over 18 cm of the length of the forearm and was as much as 7 cm in breadth. The soreness lasted for several hours. An interval of several days was allowed to intervene to ensure complete recovery, when stimulation of the same intensity and duration was repeated at exactly the same point. The area of soreness when finally mapped out corresponded closely with that previously recorded, similarly extending up the arm and covering the three veins. Other repetitions on subsequent occasions gave the same result.

Speaking generally of the effects of faradic stimulation of the forearm, it may be said that the example here presented is of a full reaction, strong stimulation of 5 min duration is followed in most individuals by less extensive effects than that described. The effects are repeated when the same spot is stimulated from time to time. The area of soreness always has its long diameter in the length of the arm, in general, it spreads proximally more

than distally when the stimulated point lies near the wrist, and distally more than proximally when the stimulated point is near the elbow. Its extension to skin overlying large superficial veins has been noted repeatedly and spontaneously by different subjects, usually the extension is up the veins, but it may be down them, or the skin over a vein may form a long lateral border of unusual soreness. A relation to veins is not invariable, but it is frequent enough to be more than accidental. It is usual to find a little

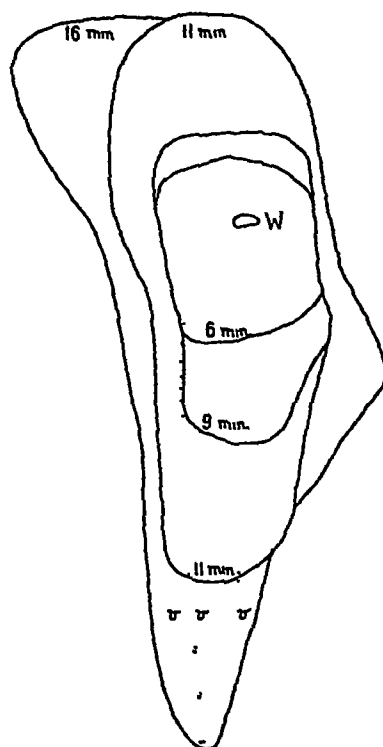


Fig 1 ($\times \frac{1}{2}$) Faradic stimulation of skin a little above the wrist T.L. February the 12th, 1935 The wheal produced is shown at W The area of hyperalgesia, which developed subsequently, is indicated by solid lines, with the times in minutes at which the corresponding outline was mapped out v, v, v indicate the centre lines of three subcutaneous veins The marks made on the skin have been traced in the case of this and similar diagrams on cellophane laid down subsequently on the arm

In this and subsequent charts the top edge of the chart represents its distal margin

soreness at the end of 5 min stimulation or for soreness to begin to develop within a minute or two Full reactions develop completely by the 15th to 30th min When widespread, it is easy for the subject to recognise that the intensity of soreness is in general greatest in skin immediately surrounding the stimulated point, and that it diminishes in degree as it is traced away from this point It lasts for different periods in different individuals and according to its original intensity, in full reactions, it is usually still recognised 8 to 12 hr subsequently, and sometimes for a period of one or two days

Description of the hyperalgesia The soreness is noticed when the skin is very lightly rubbed with a finger or other object. As a rule it is not so conspicuous that attention is constantly called to it by the contacts of clothing, but it is quite distinct. Minor grades of soreness are difficult to outline with accuracy. Sometimes soreness may be so developed as to draw frequent attention to itself, the friction of clothing being unpleasant, such soreness is often quite sharply defined.

If the area is tested by light touches with cotton wool, or by very light Frey's hairs, the sense of touch is found to be unchanged or more frequently, and usually in the early stages of the reaction, to be diminished. Needle pricks give unusually intense, diffuse, and long lasting pain. When the needle is mounted on a suitably flexible hair as handle, pricks are more often felt over the sensitive area than over normal skin. A Frey's hair which gives rise to a sense of touch on normal skin often produces a sense of pricking on the sensitive skin, and cotton wool rubbed lightly over the surface may elicit soreness.

When there is full soreness a sense of very slight spontaneous burning or smarting is felt diffusely over the whole area, this smarting is often exaggerated or develops, in response to slight friction, precisely over the area rubbed. An increased response of the pain nerves to warmth has been suspected or detected on a number of occasions on which it has been tested, but the effect when present is slight.

Spread of hyperalgesia by diffusion, etc Reasons have been given in an earlier paper for believing that in injuries of the skin a substance is released at the injury and gives rise to local tenderness and pain. Now faradism injures the skin locally and at first the idea was entertained that the zone of skin surrounding the point faradised becomes hyperalgesic owing to the diffusion or convection of a released substance, this idea was encouraged by the gradual spread of hyperalgesia from the centre, which is the rule, and by its occasional and peculiar involvement of veins, which suggested flow up lymphatic channels. But doubts arose when very large areas of skin were found to be involved in relatively short periods of time, since the spread was altogether too rapid for a movement of a released substance through the skin and since the spread might occur much farther in a distal than in a proximal direction, and when it became clear that involvement of veins is not always on the proximal side of injury. A simple experiment disposes of the idea that movement of tissue fluid plays any appreciable part. The circulation to the forearm is arrested by means of a pneumatic cuff distended upon the forearm. The faradic stimulus is now applied immediately distal to the cuff. Hyperalgesia develops at its usual rate on the ischæmic skin below the cuff. When this is well developed a second cuff is used to arrest the circulation in the upper arm, the first cuff being rapidly removed and the skin beneath it tested. This skin is found to be hyperalgesic over large areas extending upwards from the site of injury, and these areas of hyperalgesia remain unchanged for hours after the circulation of blood and

lymph is released This result led on to the testing of spread in the nervous system

The effect of blocking the relevant cutaneous nerve The nerve usually used has been the anterior branch of the external cutaneous, which supplies the skin on the front of the outer parts of the forearm This nerve is easily found by applying a faradic current to the arm (14), and its course traced and marked for a sufficient distance beneath the skin after its emergence from the deep fascia The blocking experiment should be conducted on a subsequent day, since some hyperalgesia may develop after the faradism used in testing the arm The nerve is easily anaesthetised, if it has been marked out accurately,

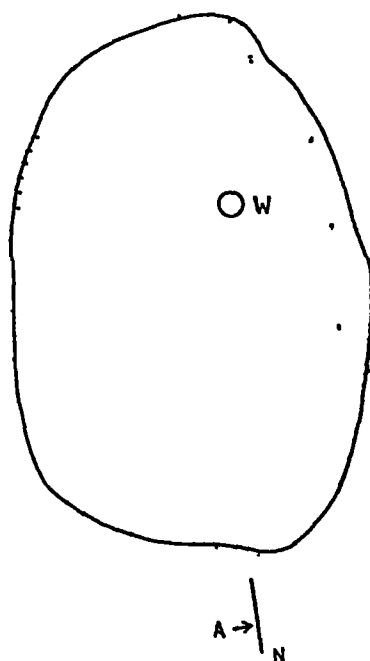


Fig 2 ($\times \frac{1}{2}$) Faradisation of skin and nerve block T L April the 22nd, 1936
 0 min A branch of the external cutaneous nerve (N) is anaesthetised by injecting 1% novocaine at (A)
 6 min An area of anaesthesia and hypoaesthesia of the skin has appeared, and the bounds of defective sensibility have been mapped out (dotted line)
 8 min The skin is faradised with a current of usual strength, sufficient to produce and maintain local goose skin for 5 min in the centre of the anaesthetic area The current is not felt It subsequently produces a wheal (W)
 21 min The nerve block is recovering and hyperalgesia is taking the place of hypoaesthesia and anaesthesia
 45 min The area of fully developed hyperalgesia is mapped out (solid line)

by introducing 0.5 c.c. of 1% novocaine 0.5 cm. and 0.5 c.c. 1.0 cm. deep into the skin in the line of the nerve The area of defective sensibility is mapped out, and a central point of absolute anaesthesia and analgesia, if present, is chosen for stimulation The stimulus is of the usual strength and duration As the nerve anaesthesia disappears the subject often becomes

aware of a little sense of burning in the skin of the arm in the region of stimulation or more diffusely, and hyperalgesia of usual extent and intensity (Fig 2), is soon displayed and lasts as usual for many hours

This experiment shows that the appearance of the hyperalgesic state is independent of the receipt of painful impulses by the central nervous system and strongly suggests it to be the result of a local mechanism

The hyperalgesia arises through nervous channels When the skin of the forearm is stimulated hyperalgesia develops around it in a zone of roughly oval form This is so wherever the stimulus is put down, and there is no clear indication that nerve districts, spinal or peripheral, are controlling the distribution The fact that nerve districts are actually involved is only indicated when the stimulus is put down in the centre of an area previously mapped out as corresponding to the distribution of a cutaneous nerve, and put down at a point known to be rendered anæsthetic by the anæsthetisation of this nerve The area of hyperalgesia produced by faradism, and the area of defective sensibility produced by nerve anæsthetisation, are frequently found to correspond with an accuracy beyond the possibility of simple coincidence Such divergences as occur between the two boundaries in the circumstances of the experiment are readily to be explained by the difficulty in mapping out one or other with great precision on the skin, or by hyperalgesia failing to develop to the full extent of the nerve's distribution It will become more and more evident that the distribution of peripheral nerves controls that of hyperalgesia as this paper proceeds That the spread is through nervous channels is conclusively shown by local anæsthetisation of the skin

The effect of preliminary local anaesthesia The skin is injected intradermally with 1% novocaine to produce a crisp wheal about 1 cm in diameter, and an equal amount of anæsthetic may also be introduced immediately beneath this wheal to paralyse any deeper lying fibres The faradic current in its usual strength is applied for 5 min to the centre of the wheal This stimulation should not be felt, or at the most should be appreciated as a slight and painless local tingle Such local anæsthetisation of the skin, while it lasts, prevents hyperalgesia developing If, after stimulation has ended, the wheal is tested with a needle, it will be found to be completely analgesic, but after 5 or more minutes this analgesia will begin to recede at its margin, a recession which slowly continues The surrounding skin shows no change in sensibility until the skin on which the electrodes actually lay becomes sensitive again There is notable correspondence in time between this recovery of the anæsthetic area at its centre and the first appearance of hyperalgesia in the surrounding skin, and from this time the hyperalgesia spreads at its usual rate to occupy a larger and larger area In these tests the novocaine injection delays the appearance of hyperalgesia for periods up to 10 or 20 min, according to the duration of anæsthesia, it delays its appearance for longer times if adrenaline is added to the novocaine solution. Ultimately the hyperalgesia is as conspicuous and as extensive as in control observations It is here to be stated that in all subjects used in these tests,

the effect of local anæsthetisation of the skin has been observed as a control, the area of skin actually injected becomes tender on recovery, and in two of these subjects small patches of adjoining skin also became sore, but the areas involved were very small by comparison with those becoming hyperalgesic in the main experiment, and the hyperalgesia when present was much less in degree and short lasting

This experiment is important from several points of view. The failure of hyperalgesia to appear while the anæsthesia holds shows that the hyperalgesic state is not due to the spread of substances into surrounding skin or to the direct spread of current to the nerves in surrounding skin. The direct effects of the faradic current are in fact very local, it is surprising how small an area of local anæsthetic cuts out all pain and goose skin during stimulation, and prevents the development of all hyperalgesia while the anæsthetic lasts. The conclusion already reached is confirmed that the development of the hyperalgesic state is independent of the receipt of painful impulses by the central nervous system. The failure of hyperalgesia to appear while the anæsthetic holds, and its development as the anæsthetic disappears, shows that local injury to the skin by faradism is primarily responsible, that a substance locally released by this injury remains, or is produced continuously at the injured point, and that this begins to act through the nerves immediately these channels are open, thus producing the hyperalgesic state of skin at a distance.

Local anaesthesia, other experiments If the skin is first submitted to faradic stimulation and the hyperalgesia is allowed full time to develop (20th to 25th min), then thorough local anæsthetisation of the skin which has been stimulated is without effect upon the hyperalgesia, and no change is detected in the area or intensity of the hyperalgesia while the local anæsthetic lasts. The duration of the local anæsthetic may be prolonged by repeating the injection, or by employing novocaine solution containing adrenaline also. In many experiments the local anæsthetic has lasted 15 or 20 minutes, in some for an hour, in some the area of skin anæsthetised has been increased to fully 2 cm diameter, the result has been uniform in all these experiments, hyperalgesia persists.*

Now it has been concluded that in the basal observation the hyperalgesia is an after-effect of local damage and supposedly arises from a local release of injury products and their action on surrounding skin through nervous channels, further evidence of the intervention of injury products will be given later. From the present experiment it is concluded that once this hyperalgesic state is established, its maintenance over considerable periods of time does not require a continuous flow of nervous impulses from the original centre of disturbance. We arrive at the interesting conclusion

* With one exception. In this a not very extensive area of hyperalgesia became reduced in one direction, the reduction was found to be due to the appearance of an area of hypæsthesia, the local injection of anæsthetic had been large and apparently a subcutaneous nerve twig was caught and paralysed. This instance is recorded as it is clearly a complication that may occasionally arise.

that the original injury sets up, through nervous channels, a relatively stable state conducing to hyperalgesia in skin lying at a distance. How this state is set up will be discussed later.

If the skin is first faradised and anæsthetised at once and before any hyperalgesia has developed, the appearance of hyperalgesia is delayed until the local anæsthesia has disappeared. This is to be interpreted in the sense that the local effects of the faradic current, on which the distant hyperalgesic state ultimately depends, are not established immediately in the case of faradism, but are cumulative, or to particularise, the products of local injury are not released fully and at once.

If the skin is first faradised and hyperalgesia is allowed to develop partially (9th to 11th min.) local anæsthetisation fails to impede or to reduce its further development. Thus the effect produced through the nerves on distant skin is seemingly one which once started develops further.

Nerve block and local anæsthesia. In considering the effects of a skin injury we dealt first with the possibility of painful impulses acting on the central nervous system, there is another way in which the central nervous system might conceivably be affected, namely, by painless impulses. When the nerve to the skin is blocked before that skin is stimulated, painless impulses might nevertheless ascend to the central nervous system after the recovery of the block and might be conceived to set up in it a process by which tenderness was referred to the periphery. This possibility is ruled out, and the alternative hypothesis of a purely local process proved, by the following experiment. The nerve is first blocked and the faradic stimulation carried out painlessly. Ten minutes are allowed to elapse, so that the supposed change that is conceived to occur in the skin surrounding the injured area may be well started, and the damaged area is now thoroughly infiltrated with novocaine and adrenaline. Impulses can travel to the end of ten minutes interval in the peripheral nervous channels, but are barred from reaching the central nervous system, subsequently they are barred from emerging from the damaged area. The result is the expected one, when the nerve block recovers—and it tends to recover first because put down first and without adrenaline—the usual area of hyperalgesia is found surrounding the still analgesic area of injury. In this experiment it is a little difficult to arrange that recovery from the nerve and the local anæsthetic should occur at appropriate times, but it has been carried out repeatedly with full success, and with the result stated, on two subjects (Fig. 3). It seems to provide conclusive evidence that the hyperalgesic state is not generated through the central nervous system.

Hyperalgesia following mechanical injury

In subjects in whom hyperalgesia is easily produced by strong and prolonged faradisation of the skin, an exactly similar hyperalgesia can be produced by crushing little bits of the living epidermis. A fold of the skin, as small a piece as can be held, is caught up at the tip of a pair of strong but

finely tapered forceps, is abruptly crushed and the forceps removed * Hyperalgesia appears very quickly, it may be recognised within periods as short as 10 sec from the injury The hyperalgesia is at first in the skin directly surrounding the broken skin, but it spreads rapidly during the next 3 or 5 minutes, and more slowly up to the 10th to 15th minute Not

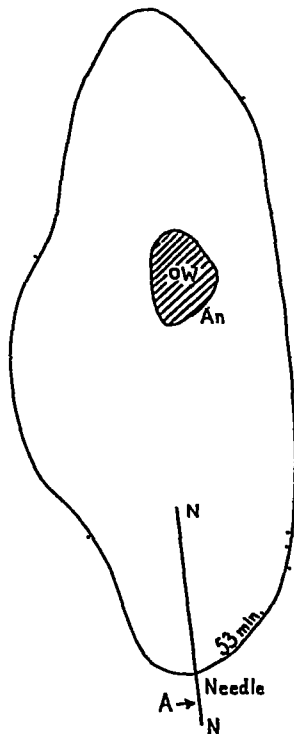


Fig 3 ($\times \frac{1}{2}$) Faradism of the skin after blocking the nerve to it and with subsequent local anæsthesia T L May the 1st, left forearm The position of the anterior branch of the external cutaneous nerve is shown at N N as mapped on the skin

- 0 min The nerve is anæsthetised by piercing the skin over it at point marked "needle" and injecting 1% novocaine in the region of the nerve at A The area of resultant anæsthesia and hypoæsthesia is indicated by the dotted outline, it includes a small area of skin anæsthetised by direct infiltration near the injection
- 4 min The centre of the area of anæsthesia is faradised for 5 minutes at W, the current is not felt The stimulus produces goose skin
- 19 min The nerve block is still full 1% novocaine with adrenaline injected into the skin intradermally and a little subdermally at the site of faradic stimulation
- 30 min The nerve block has recovered, leaving a central area (An) anæsthetic from the local injection Distinct sense of burn around the faradised region Hyperalgesia has appeared over a wide area, which subsequently increases and is represented by the solid line at the 53 min the local anæsthesia persisting

* Many years ago Goldscheider (2, 3) reported that hyperalgesia appears around a fold of skin pinched by a small clamp This hyperalgesia was associated with the pain produced by clamping, it disappeared when the clamp was removed His investigations were made during the period of painful clamping My observations concern hyperalgesia following as a long-lasting after-effect of injury I have not investigated the phenomenon described by Goldscheider and cannot bring his observations into relation with my own

infrequently it tends to pick out skin over large superficial veins. The full area of hyperalgesia is less than that found after 5 minutes of faradism, being rarely more than from 5 to 10 cm in length, but areas of 15 to 20 cm length are sometimes seen. The hyperalgesia lasts for several or many hours.

These areas of hyperalgesia are unaffected by thoroughly anæsthetising the region of injury by intradermal and subdermal injections of novocaine, the test is particularly satisfactory in the case of this injury, which is so easily and quickly covered by anæsthetic. If the skin is crushed after the local anæsthetic has been put down, no hyperalgesia develops until the local anæsthesia has disappeared. In these respects the reactions are precisely like those already described for faradism. A difference is displayed if the local anæsthetic follows quickly upon the crush or upon the faradic stimulation, in the latter instance hyperalgesia fails to develop, whereas in the former case it develops fully and at a rate that appears to be but little changed by the local injection, even if this is completed within 15 seconds of the injury.

These experiments support the view that damage to the cells of the skin and local release of a tissue substance is responsible for the subsequent hyperalgesic reaction. The speed with which hyperalgesia develops in the case of the crush, relative to that in faradisation, is explained by supposing the almost instant release of substances locally. The injury is effective when the smallest fold of skin is crushed, an indication that the substance released may be derived from the epithelium.

It is of interest to note that subjects who fail to develop hyperalgesia after faradic stimulation fail to develop it after the crush and that in both instances surrounding hyperalgesia may be replaced by hypoaesthesia or by itchy skin.

Hyperalgesia following freezing

Freezing is another and useful method of damaging skin, for it is painless and the severity of injury can be graded nicely and at will. New experiments on the effects of freezing have been undertaken but their description will be deferred (page 403). Here I will confine myself to stating the immediately relevant facts that widespread hyperalgesia of the usual type develops around these freezes, and that the hyperalgesia appears quickly when the freeze is severe, but may take hours to develop when damage is slighter. The appearance of widespread hyperalgesia in these experiments may be interpreted as resulting from damage to the walls of the cells during their solidification and to subsequent release of appropriate substances into the intercellular spaces. Such an interpretation has already been used to account for the triple response which follows at once after freezing skin and is attributed to the release of H-substance.

The appearance of hyperalgesia seems to be associated with the severer grades of injury, such as disrupt the cells, as is the case with the crush or the severe freeze, in which case hyperalgesia comes quickly, or with less

severe forms of damage that are prolonged, and lead to the development of hyperalgesia as a delayed effect, as in the case of faradic stimulation or of the mild freeze

Skin extracts and hyperalgesia

I find that if freshly excised human or guinea-pig's skin is extracted by crushing it, or by freezing and then crushing it, and by adding an equal or smaller bulk of distilled water to the pulp, the fluid so obtained after centrifugalisation, gives rise to local smarting when injected in small quantities (0.02 or 0.03 c.c.) intradermally. The smarting comes after a short delay and increases in intensity, it is usually mild but may be severe and lasts usually for several minutes. It is sometimes mixed with itching, for the juice expressed from skin in this way contains H-substance and wheals the skin into which it is introduced, as previously shown in this laboratory. Hyperalgesia soon develops around the site at which this juice is injected, and it spreads for about 10 to 15 min. The full areas of hyperalgesia may be extensive.

Many experiments have been conducted on these lines. They are consistent with the belief that a substance is present in normal skin, which, when released, is capable of giving rise to hyperalgesia and to pain. Observations in which Professor C. R. Harrington has given me his help show that the extract does not owe its potency to changed pH or to altered tonicity. The pain is not due to contained protein, which may be removed without affecting the reaction, to potassium, or to histamine, or to acetylcholine*. But I think it would be unjustifiable to press these observations in favour of the main thesis, owing to the complex nature of the fluid introduced, it will be wise to wait until a substance has been isolated.

PART II HYPERALGESIA FROM STIMULATION OF CUTANEOUS NERVE TRUNKS

The effects hitherto described are due to injury of the skin, they are not much contributed to by direct stimulation of small nerve branches in the skin, for if that were so the effects developing after stimulating skin,

* The pH (natural or adjusted) of extracts of skin giving positive results has varied between the limits 5.8 and 7.8. Buffered solutions, prepared by using disodium hydrogen phosphate and phosphoric acid to form an isotonic solution and of pH 5.8, 7.0 or 8.0, have been injected intradermally in doses of 0.02 or 0.03 c.c. into the same subjects, and gave little or no effect. Occasionally there is a very slight sting directly after the injection and lasting for a few seconds only.

Extracts of skin of pH 7.5 and having freezing point depressions equivalent to 0.73, 0.9 and 1.38 % sodium chloride have given the usual effects. Injections of the same quantities (0.03 c.c.) of 1% and 2% sodium chloride are without effect, a 3% solution brings a slight sting after 5 or 10 seconds, lasting about a minute.

Potassium chloride, 0.3% made isotonic with sodium chloride and injected in same quantities is without effect, a 0.6% solution gives stinging pain lasting 15 or 20 sec.

Histamine phosphate, 1 in 100,000, buffered with disodium phosphate and phosphoric acid, isotonic and of pH 7.0 to 7.5, when injected in the same doses is followed by simple itching of the skin.

Acetylcholine, 1 in 10,000, buffered to pH 6.6, isotonic, and used quite fresh, gives no effect.

which has been locally anaesthetised, would be reduced appreciably or abolished. I emphasise this fact here for the reason that I am about to describe experiments showing similar effects to be obtainable by stimulating nerves. The two series of experiments must be kept separate owing to the different ways in which hyperalgesia originates. The more dramatic effects of this second series should not be allowed to obscure the greater importance and more immediate relevance of the first series to hyperalgesia arising pathologically. Faradic stimulation of nerves is a wholly artificial procedure, injuries of the skin giving rise to wide areas of surrounding hyperalgesia are frequent events.

Faradisation of nerve trunks

The nerve used has usually been the anterior branch of the external cutaneous nerve of the forearm shortly after it emerges from the deep fascia. It is found by applying a faradic current to the forearm, moving the electrodes about until the characteristic fluttering along the course of the nerve is felt, as first described by Trotter and Davies (14). The course of the nerve is followed up and down the forearm and marked for future use. Now, in stimulating the nerve through the skin it is obvious that some of the effects may be those of local skin injury as previously described, but preliminary observations showed that the application of a faradic current of a given strength produces much more profound effects when it is applied over a nerve than when it rests on skin only. If it is desired to produce a widespread hyperalgesia it is usually necessary, in subjects susceptible to the production of hyperalgesia, to stimulate the skin for 5 min. Hyperalgesia as widespread can usually be produced in the same subjects by current of the same strength applied over the nerve for 1 minute. Stimulation of the skin for 1 minute produces an oval patch of hyperalgesia of no great extent, stimulation a centimetre from the same point but over the cutaneous nerve produces hyperalgesia extending often throughout the whole of the nerve's territory. Faradisation for 1 min., or in certain instances 2 min., over the nerve, at the current strength just necessary to evoke definite surrounding goose skin, has been the stimulus.

The hyperalgesia so produced does not differ in character from that previously described on page 377. The area involved may be less than that of the nerve's cutaneous distribution or it may fill this distal territory completely and very accurately, as shown by comparing the area with that of diminished and lost sensibility after anaesthetising the same nerve. The proximal parts of the area usually tend to become hyperalgesic first and the distal areas to follow, sometimes a band of hyperalgesia has been noted within and in the whole length of the nerve territory, a band which broadens later by lateral addition to it. The hyperalgesia develops to its maximal degree and extent in about 10 to 15 minutes from the end of stimulation, it is maintained for 2 to 4 hours after stimulation lasting a minute, and after stimulation lasting several minutes it is maintained till next day. It is

frequently associated with a slight but distinct sensation of smarting in the skin, which may be brought into evidence or exaggerated by light friction of the affected skin

If the cutaneous nerve is mapped out and marked over 5 or more cm of its course, the effects of stimulating the nerve below and above a nerve block may be tested. Accurate surface marking is necessary, so that the

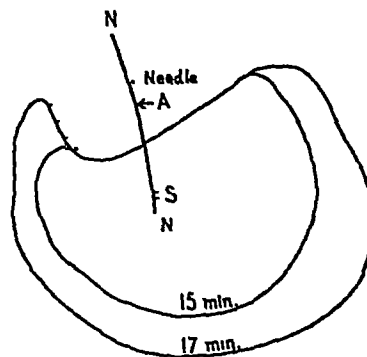


Fig 4 ($\times \frac{1}{2}$) Stimulation of anterior branch of the external cutaneous nerve (N) through skin, nerve blocked below T L, left forearm, May the 8th

- 0 min The region of the nerve was injected at A with 1 c c of 1% novocaine
- 6 min Area of anaesthesia and hypoaesthesia fully developed and mapped out (dotted line)
- 8 min Faradic stimulation at S, with coil at usual strength, for 2 min, goose skin maintained in surrounding skin throughout. The stimulus very painful locally and fluttering pain felt during the whole period along the nerve's territory
- 15 min An area of hyperalgesia has developed around the point of stimulation and is charted
- 17 min The nerve block is recovering. The area of hyperalgesia has increased a little
- 19 min A little spontaneous burning felt around region of stimulation, but nowhere else, the nerve block has quite recovered and skin sensation in the corresponding area is perfectly normal and remains so for the next hour of observation

nerve can be anaesthetised with small quantities of 1% novocaine and quite locally (the usual dose is 0.5 c c at a depth of 0.5 cm and 0.5 c c at a depth of 1 cm), and so that the faradic stimulus shall not fail to reach the nerve subsequently. After a little practice the experiments are done successfully

and without difficulty and a large series has been carried out with remarkably uniform results

The effect of nerve block below The nerve is stimulated through the skin, after it has been blocked 2 or 3 cm below the point of stimulation and the resultant anaesthesia is complete. In every experiment of this kind the current has been continued for the full period of 2 min. Subsequently an area of hyperalgesia develops, as is to be expected, immediately around the point of stimulation (Figs 4 and 6), it usually develops completely before

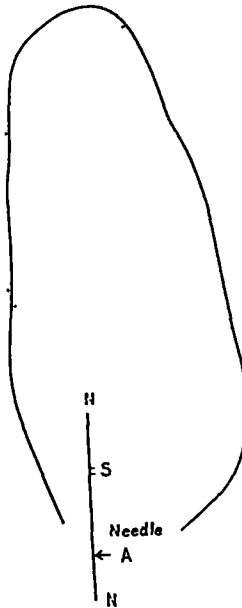


Fig 5 ($\times \frac{1}{2}$) Stimulation of nerve through skin, nerve blocked above T L left forearm, April the 28th. The course of the anterior branch of the external cutaneous nerve had been marked on the left forearm days before.

- 0 min The region of the nerve injected (at A) with 1 cc 1% novocaine the needle being inserted where shown
- 5 min The resultant area of anaesthesia and hypoesthesia has fully developed and is mapped out (dotted line)
- 9½ min Faradic stimulation at S in line of nerve for 2 min. Current of usual strength goose skin throughout stimulation in surrounding skin. The current felt as a slight local tingle, no fluttering along the nerve. At the end of stimulation the area of anaesthesia and hypoesthesia is unchanged in extent and degree
- 25 min The anaesthesia and hypoesthesia have disappeared and a large area of hyperalgesia has appeared (solid line)

the nerve block recovers. When this block clears away, no hyperalgesia is found to develop within the territory of the nerve's distribution, and no smarting is felt there.

Although the sensorium receives painful impulses for a long period, no peripheral after-effect is discoverable if the pathway between the point

of stimulation and the periphery is blocked. Thus, so far as the somatic nerves are concerned, the experiment provides evidence against the view that an irritable focus is set up in the spinal cord or in any other part of the central nervous system, and suggests that a peripheral mechanism is responsible for diffuse hyperalgesia arising out of nerve stimulation. That this is actually so is proved by the next experiments.

The effect of nerve block above. The place at which the nerve is to be stimulated being chosen, the skin is marked at the precise points on which

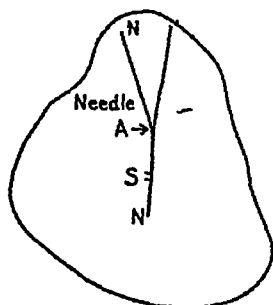


Fig 6 ($\times \frac{1}{2}$) Stimulation of nerve through skin, nerve blocked below. A.J.H., left forearm, April the 29th. Anterior branch of external cutaneous nerve, sending out a branch to the right in the diagram. The nerve was blocked near the origin of the branch, and was stimulated with the usual current for 2 min. at *S* through the skin. The current was very painful, being felt both locally and in the distribution of the nerve. Dotted line is area of anaesthesia and hypoaesthesia from the nerve block. The solid line marks the full area of hyperalgesia, which developed subsequently.

the two electrodes must lie for the stimulation to be effective. The points should be marked hours or days beforehand, and checked at the time of observation by putting the electrodes in place and turning on the current for an instant only. The nerve is now anaesthetised 2 or 3 cm proximal to the chosen point, stimulation is begun when anaesthetisation is complete and the area of defective sensibility has been marked out on the skin. When

the nerve has been blocked successfully no flutter and no pain is felt along its distribution during the stimulation. The current may not be felt at all, but more usually a little tingling is perceived at the point where it enters the skin, stimulation is maintained for 1 or 2 minutes at the standard strength. When the nerve block recovers, 15 to 60 min after stimulation has been completed, hyperalgesia is found filling the whole or a large part of the area already mapped out as that of the nerve's distribution (Figs 5 and 7). In its extent this distal area of hyperalgesia is equal to, or sometimes a little smaller than, that given by control stimulation of the unblocked nerve, and

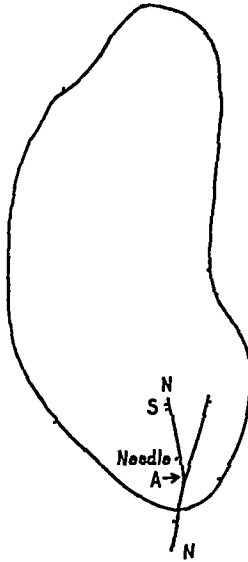


Fig 7 ($\times \frac{1}{2}$) Stimulation of nerve through skin, nerve blocked above. A J H, left forearm, May the 8th. Same nerve as shown in Fig 6. The nerve was blocked near the origin of the branch. It was stimulated for 2 min at S through the skin, only a tingle and that slight, was felt at the electrodes. The dotted line maps out the anaesthesia and hypoesthesia from the nerve block. The solid line marks the full area of hyperalgesia, which developed subsequently.

The area of hypoesthesia lay along the radial border of the arm and the difference in its relations to the nerve in this and the preceding diagram is partly due to varying error in transferring the outline from the curved to a plane surface on the two occasions.

it is greater than the area of hyperalgesia obtained in a second control in which the skin is stimulated close to but not over the nerve. The hyperalgesia following stimulation of the blocked nerve is of usual intensity and duration.

In this experiment the point at which the stimulus is applied lies well within the proximal part of the area subsequently showing hyperalgesia.

(Fig 7), and it will be obvious that this proximal part of the area may be a response to cutaneous damage rather than to direct stimulation of the nerve. To differentiate between the extent of the two forms of response, the control stimulation of skin is used for comparison, as previously indicated. A different method may be used, namely, stimulating the nerve directly and not through the skin.

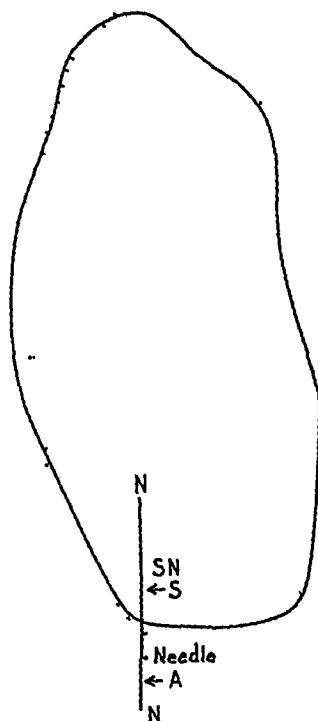


Fig 8 ($\times \frac{1}{2}$) Direct stimulation of nerve, nerve blocked above T L, left forearm, May the 22nd. The anterior branch of the external cutaneous nerve.

The stimulating needle was inserted through the skin at SN, to reach the nerve in the region of the arrow S.

- 0 min Region of nerve injected at A. Stimulating electrode tested.
- 4 min Nerve block fully developed, area of anaesthesia and hypoaesthesia mapped out (dotted line).
- 7½ min Nerve stimulation begun and continued for 2 min. Stimulation not felt, no goose skin.
- 15 min Nerve block beginning to recover.
- 30 min A diffuse but distinct burning is felt approximately in area of skin covered by the nerve. Nerve block recovered, the skin is now hyperalgesic.
- 39 min Area of hyperalgesia (solid line) fully developed. The mapping out of hypoaesthesia and subsequent hyperalgesia were regarded at the time as being unusually precise.

Direct stimulation of nerve trunks. A fine hypodermic needle is thrust $\frac{1}{2}$ cm through the skin over the line of the nerve, a fine enamelled copper wire is passed down the needle to a marked point, which ensures that the wire just projects from the end of the needle. This forms one electrode, and the second is formed by a broad contact on the dorsal surface of the same forearm.

A very weak faradic current is passed and the position of the needle electrode adjusted until fluttering is felt along the nerve trunk, the passage of the current is instantly stopped. The secondary coil is moved up about 3 cm and stimulation repeated for an instant, this should give for an instant a fluttering pain in the nerve. Anæsthetic is then injected into the region of the nerve trunk 2 or 3 cm above the stimulating electrode, and the stimulating electrode tested again momentarily to ensure that it is well placed, before the anæsthetic takes effect. When the latter has happened the experiment proceeds as in the case of nerve stimulation through the skin. The faradic

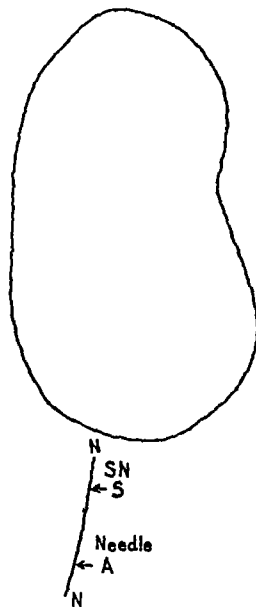


Fig 9 ($\times \frac{1}{2}$) Direct stimulation of nerve, nerve blocked above R H, left forearm Nn1 the 22nd The anterior branch of the external cutaneous nerve

Stimulating needle electrode inserted at SN to stimulate nerve at S. Nerve injected in region A with 1% novocaine. The nerve stimulated, after the nerve block was complete for 2 min, a little local tingling alone felt. The solid line shows the area of hyperalgesia developing after the nerve block recovered.

current is passed for 2 min, it may give a very little tingle locally, or may not be felt at all. When the nerve block recovers, slight but distinct smarting of the skin is sometimes felt, and the greater part or the whole of the area of the nerve's distal distribution is always found to be hyperalgesic (Fig 8). But in this experiment hyperalgesia does not widely surround the electrode on all sides as it does when the skin has also been stimulated (compare Figs 8 and 9 and Fig 7), and frequently the whole area of hyperalgesia lies at a distance from the stimulated point (Fig 9).

PART III HYPERALGESIA FROM STIMULATION OF SMALL NERVES, ETC

The 5th cranial nerve

In three subjects tenderness in the skin has been produced by stimulating the mucous membrane of the lower lip within the mouth. A faradic current is employed at painful strength and is passed through twin electrodes for 2 or 3 min. This stimulation is followed by a sense of slight but distinct burning in the lip. Hyperalgesia begins to be distinct in about 15 min from the beginning of stimulation and develops during the next 15 min. Its extent is variable, but it includes the whole inner surface of the lower lip and may involve the whole of the corresponding skin with the skin of the chin, but the effect has not been observed to spread across the middle line.

The following observations upon the maxillary antrum have been carried out on myself only. Twenty years ago the left antrum became infected and was cured by draining it into the nose through a hole cut in the lower part of its inner wall. A curved probe can still be passed easily into the cavity and its interior explored. Contacts give no sense of touch, but of a little uncomfortable soreness, like that experienced from the rest of the nasal mucous membrane. The discomfort is felt diffusely in the left side of the face, the contacts cannot be located accurately, thus, it is impossible to be sure from subjective sensation whether upper or lower, outer or inner, wall is being touched. The cavity of the antrum has been explored and stimulated repeatedly with suitably curved electrodes. When the electrodes are directed towards the lateral and lower parts of the antrum the current flows into different dental branches of the infraorbital nerve and gives rise to characteristic painful aching in different teeth. A strength of current easily tolerated on the tongue is barely tolerable over the nerves within the antrum, it has been used at this strength. Over simple mucous membrane stronger current has been employed. The current is passed in any experiment for about 3 min.

When stimulation ends, nothing unusual can be felt and sensation in the skin of the face is quite unchanged, sometimes a patch of numbness is found for a time upon the front part of the palate. About the 8th to 10th minute a little burning comes in the region of the left malar process and in the lower eyelid. The lower eyelid, and a little later the malar region, are the first parts to exhibit soreness and here soreness continues to be most conspicuous. The degree and extent of hyperalgesia increase, most of the cheek is involved, a little of the temple, the ala of the nose, and in a minor degree the whole of the skin of the upper lip. The hyperalgesia reaches its height in about 40 to 60 min from the beginning of stimulation, it continues until next day, but is then diminishing, the slight burning is felt for hours, it is exaggerated by touching the face. The slow development and long duration of the hyperalgesia are remarkable. The area involved is shown in Fig 10, it corresponds to the whole cutaneous distribution of the maxillary division of the 5th nerve. It has never extended to the first

or third division of the 5th nerve nor to the opposite side of the face. Tenderness of palate, and mucous membrane of gums or lips within the mouth has not been found, but the exposed mucous membrane of the lip becomes a little sore. A little soreness of the eye, reminiscent of similar soreness complained of in influenzal colds, may be experienced when the eyes are moved, but this is unusual. The distribution of burning and of soreness, their time and order of onset, and their duration are the same, whether the nerve to the incisors or to the molars or whether the mucous membrane is stimulated, provided the stimulus is adequate.

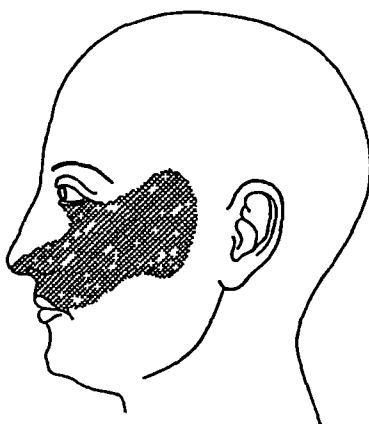


Fig. 10 A diagram of the face showing the area of hyperalgesia developing on stimulating the mucous membrane or dental nerves within the left maxillary antrum.

Sometimes during the reaction the left malar process acquires a slightly greater flush than the right one, but the effect is inconspicuous, and I have been unable in very careful tests to determine any definite and constant rise of temperature in the cheek.

It has happened twice, since these experiments on the antrum have been done, that I have acquired a simple nasal catarrh. As is usual on such occasions the secretions of the nose are a little increased for a day or two, and a little muco-pus accumulates on the left side, but left side only. I assume that this muco-pus is associated with spread of infection to the left antrum. This catarrh is accompanied by a little sense of burning in, and hyperalgesia of, the facial skin on the left side, a phenomenon with which I have long been familiar both in my own case and in the case of patients with antral infection. But these two recent attacks have allowed a close comparison between the cutaneous effects of infection and of faradic stimulation. They are indistinguishable.

These effects from the maxillary antrum illustrate important points. Firstly, local irritation within the territory of a nerve of considerable size, may induce tenderness over the whole field of this nerve's distribution,

the failure of the tenderness to appear beyond the distribution of the middle division of the 5th nerve may possibly possess special significance, but here it should be remembered that the strength and duration of stimulation has been limited. Other instances of the type of spread described in the maxillary nerve, will be described almost at once in the nerves of the hand. Secondly, such effects may arise not only under the artificial and painful stimulus of faradism, but from painless irritation or damage caused by infection, this is of special importance from the pathological standpoint. Thirdly, the effects are shown to spread from mucous membrane to skin, thus, they are not to be regarded as merely of cutaneous origin.

Small nerves of the hand

These observations on my antrum, which seemed to show that hyperalgesia may spread from a small branch of a nerve to the whole territory of the nerve, suggested further experiments on the nerves of the hand. For here in virtue of the clefts between the fingers a small nerve to one finger is conveniently separated from the nerve to an adjoining one. When stimulating one nerve there can be no question of spread of current to the other and any spread of hyperalgesia must be conveyed up one finger and down its neighbour, a minimal path, which may be measured. The experiments have been carried out repeatedly on the same or different nerves of my own hand and that of A J H, with uniform results.

Ulnar area. The first nerve twig used was the digital nerve running on the radial border near the palmar surface of the little finger. This nerve is easily found with a faradic current and stimulation of it gives a sense of painful fluttering to the tip of the finger. Stimulation for 1 or 2 minutes at a strength giving considerable pain yields subsequent numbness of the little finger along its radial surface from the point stimulated to its tip. Hyperalgesia follows, and this spreads in about 10 or 15 mm up to the web between the 4th and 5th fingers, and in a half hour may extend along the ulnar surface of finger 4 to its tip. Such hyperalgesia lasts several or many hours. If stimulation is continued for 5 or more minutes, the current strength being raised as stimulation proceeds, hyperalgesia develops over the whole distribution of the ulnar nerve to the hand. First it involves, in the manner described, the adjacent surfaces of the 4th and 5th fingers. The next area involved is usually the dorsum of the hand, but it may be the ulnar side of the little finger. Full development occupies 30 to 50 minutes. The hyperalgesia is much less prominent on palmar surface than on dorsal surface of hand and finger, but it is sometimes quite distinct on the former. The hyperalgesia is in all respects of the type already described and it is accompanied frequently by a sense of warmth or of actual slight smarting both in the fingers and in the back of the hand. This little sense of burning is increased or brought into evidence wherever the affected surface is gently rubbed. When occupying the whole ulnar area hyperalgesia often lasts

for 24 or more hours. These experiments on the ulnar nerve area are illustrated in Plate Figs 18 and 21.

The point at which the digital nerve can be stimulated with certainty may be marked on the skin and the ulnar nerve anæsthetised at the elbow before stimulation begins. This allows stimulation to occur painlessly and the current may be increased in strength and duration. When the nerve block recovers hyperalgesia of the ulnar area is fully displayed and is conspicuous and sharply defined. The experiment has been done three times on the two subjects, and the result is in accord with the effects of blocking a nerve trunk above the point of its stimulation. The mechanism is again shown to be a local one, and the area of hyperalgesia is shown to correspond closely to the areas over which the ulnar nerve is distributed (Figs 18 and 21).

Strong stimulation of the nerve on the inner side of the 4th finger has given hyperalgesia of the whole ulnar area, with some hyperalgesia of adjacent surfaces of fingers 3 and 4, presumably by spread through the median territory.

Diffuse hyperalgesia, following stimulation of the digital nerve through the skin is in part the result of local injury to the skin, and in part the result of stimulation of the nerve twig. This is shown to be the case by two further observations. Firstly, the skin of the little finger is stimulated near to but not actually over the digital nerve, after local anæsthetisation of the skin, the current used is the usual strong current, but is quite unfelt, the nerve is not anæsthetised, but lying a little way off is also unaffected by the current. Hyperalgesia may subsequently develop over the whole ulnar area, and may be of full intensity and duration, but it is usually of decidedly less extent, less intense, and is of relatively short duration. The result is the same if no local anæsthetic is used. This observation corresponds to those recorded in Part I. Secondly, the digital nerve is stimulated by means of the subcutaneous electrode described on page 390. In this case the current used is much weaker, it is used at a strength giving strong fluttering to the tip of the finger with little or no element of pain, nothing should be felt in the skin where the electrode lies. Stimulation of this kind of 4 or 5 min. duration gives full hyperalgesia in the ulnar area subsequently.

Radial area Stimulation of branches of the radial nerve through the skin similarly give rise to areas of hyperalgesia extending over the whole territory of the radial nerve, although the nerve twig actually stimulated supplies but a small part of the territory (see Figs 19 and 20 and accompanying notes). The effects of control stimulation of the skin have been tested and found similar to those stated for the ulnar area.

Median area Prolonged stimulation of the inner side of the index finger has given subsequent hyperalgesia of the dorsal surfaces of the 1st to 3rd fingers and of the radial side of the 4th finger, as illustrated in Fig. 21. It is less distinct on the palmar surfaces of the fingers, though these may be affected too.

THOMAS LEWIS

Comment The main comment to make at this stage is upon the length of the paths through which the stimulus must travel to render distant skin hyperalgesic. It is clear that after stimulating the middle of the 5th finger, the impulses must pass for about 4 cm up the 5th finger and a distance of 7 or 8 cm down the 4th finger. The change in the skin responsible for hyperalgesia is undoubtedly produced through nervous channels and it is certain that the mechanism is purely peripheral and does not involve the central nervous system. It may be considered on the basis of the paths being collateral axons. If we discuss conveyance only through the known anatomical paths, then the impulses must pass to the dorsum of the hand from finger 5 through the palm of the hand to a point a little distance above the wrist, with descent through the dorsal branch of the ulnar nerve. The upward path cannot be much less than 15 cm, though the downward path is less. This is of course a minimal statement of the possibilities. The whole cutaneous distribution of the ulnar nerve is often involved in hyperalgesia. But this ulnar cutaneous territory is limited, if the nerve supplied skin of fore or upper arm in its course, these areas might be involved also. Moreover it is conceivable that stronger and longer stimulation might even cause spread to other branches of the brachial plexus. Briefly, the extent to which spread can happen is still unknown, but the paths we are already forced to consider are of remarkable length.

PART IV THE NERVOUS MECHANISM OF THE HYPERALGESIA

In the preceding pages three types of experiment have been described in each of which a distant state of hyperalgesia is produced, it is produced in one case by injuring the skin, in a second by stimulating the cutaneous nerve trunk, and in a third by stimulating a small branch of a cutaneous nerve. The distant effect in all three instances appears to be the same in essence. Hyperalgesia is provoked in a wide area of skin within or actually filling the cutaneous nerve territory inside which the stimulus falls. The hyperalgesic state in all three instances is independent of change induced in central nervous system or in the main nerve trunks, for in all it occurs when a barrier is set up between these nervous structures and the periphery. In all three instances the hyperalgesic state is produced through a local nervous mechanism. Because there is this in common, and because in all instances the hyperalgesia is of one kind, being associated with the sense of a little smarting in the skin, developing slowly, having a like distribution and a common order of stability, outlasting the passage of the original nervous impulses for long periods of time, I conclude that the system of nerves involved is the same in the three forms of reaction, and that, whether the original nervous impulses descend directly to the periphery, or first ascend and then descend, the same effector mechanism is called into play and establishes in the skin the same process or state. This conclusion is in my view inevitable, and I shall proceed on its basis to discuss the kind of nerves that are concerned,

and the more intimate aspects of the process by which hyperalgesia is induced

The nerves concerned

The arrangement of the nerves within the skin When hyperalgesia fills the whole territory of a cutaneous nerve in response either to a small and local skin injury, or to a stimulus applied to a nerve twig running to a

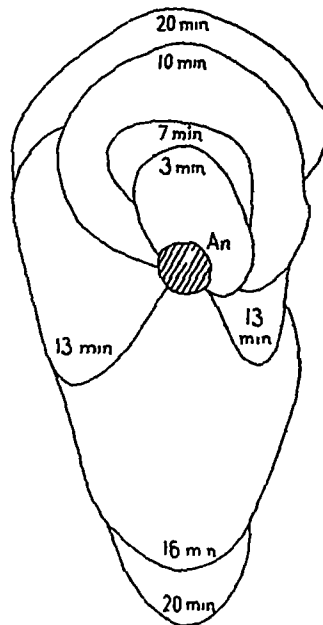


Fig 11 ($\times 2/3$) Crush placed eccentrically over anesthetised skin A.J.H., July the 18th
A circular area of skin (An) is anesthetised by intradermal injection of 1% novocaine
The area of analgesia is mapped out and it is noted that there is no surrounding hyperalgesia
skin 2 min later

- 0 min A tiny piece of skin (indicated by a dot) lying within but near the distal margin of the anesthetised area is crushed The crushing is painless
- 3 min The area of analgesia is receding at its margin, it still just includes the crushed skin An area of hyperalgesia has appeared and gradually extends to the contours marked by corresponding times
- 7 min The crushed skin is now just outside the area of receding analgesia
- 10 min Hyperalgesia still extends there is still a barrier of analgesia between the crush and the proximal skin in which sensation is normal
- 16 min The injected skin has almost recovered and by 20 min has completely recovered hyperalgesia now surrounds the crush widely in every direction

small area of skin such as one side of the end of a finger, the hyperalgesic state is provoked from a small territory to appear in a much larger one As we have concluded that this provocation occurs through nervous channels it follows that nerve paths must connect the small territory to all parts of a much larger territory Thus we are brought to conclude that the skin

possesses a system of nerve fibres connecting every part with almost every other part within the territory of a given cutaneous nerve. This conclusion holds, whether we conceive a system of simple branchings and rebranchings, or a network. In either case, if we accept the view that a nerve impulse is confined to the nerve fibre through which it is travelling, and cannot be conveyed to a parallel fibre in mere contact, we shall think of a movement of impulses from their origin to their destination through a complex and branching system of axons.

In considering experiments in which the impulses are derived from a small area of damaged skin, it can be shown they are at first conveyed in nerves lying within the skin itself. This is shown particularly well by using the tiny crush as the source of impulses. If the skin is first anaesthetised by an intradermal injection of 1% novocaine about 1 cm in diameter, and a tiny piece of skin is crushed in the middle of this, the appearance of surrounding hyperalgesia is delayed, as has been related, until the anaesthetised skin recovers, which it does first at its margin and eventually at its centre. If the crush is put down eccentrically, the anaesthetised skin in recovering soon recedes from the crush. About the time when this happens the first area of hyperalgesia appears, it comes on the side where the crush lies and enlarges, but for a time it does not invade the skin at the ends or on the far side of the barrier, and the full area of hyperalgesia does not develop until this barrier has wholly disappeared. This phenomenon has been witnessed in very many deliberately planned observations on two subjects of which Fig 11 is an illustration, and a similar phenomenon has been seen in a number of other instances in which a large barrier of local anaesthesia is put down, the crush being placed on sensitive skin quite near to it (Fig 12). It does not matter in placing the crush eccentrically whether it lies within the proximal or the distal margin of the anaesthetic area. Similarly it is a matter of indifference on which side of an anaesthetic barrier the crush is placed on sensitive skin, and it makes no appreciable difference whether the barrier is in the length of or across the arm. Almost invariably, the anaesthetised skin acts as a complete barrier to the spread of hyperalgesia beyond it, and limits the spread even on the side of the crush. But, if the crush is put down 1 cm or a little more from the barrier, then the barrier is much less effective or is without effect, hyperalgesia appearing beyond it from the start or after a little delay (Fig 13). These experiments, taken as a series, indicate the kind of arrangement that the nerves involved possess. They tend to indicate that these form arborisations rather than networks, otherwise there would be invariable spread along and around the margins of the barriers. If we picture nerve axons forming finely branching rich end-plexuses, the latter lying mainly or entirely within the skin, and the parent axons deeper and themselves running into common subcutaneous stems, the system would be adequate to explain the relatively uniform affection of the skin and the diffuseness of hyperalgesia, the gross interference caused by near intracutaneous barriers and the smaller interference caused by more distant barriers.

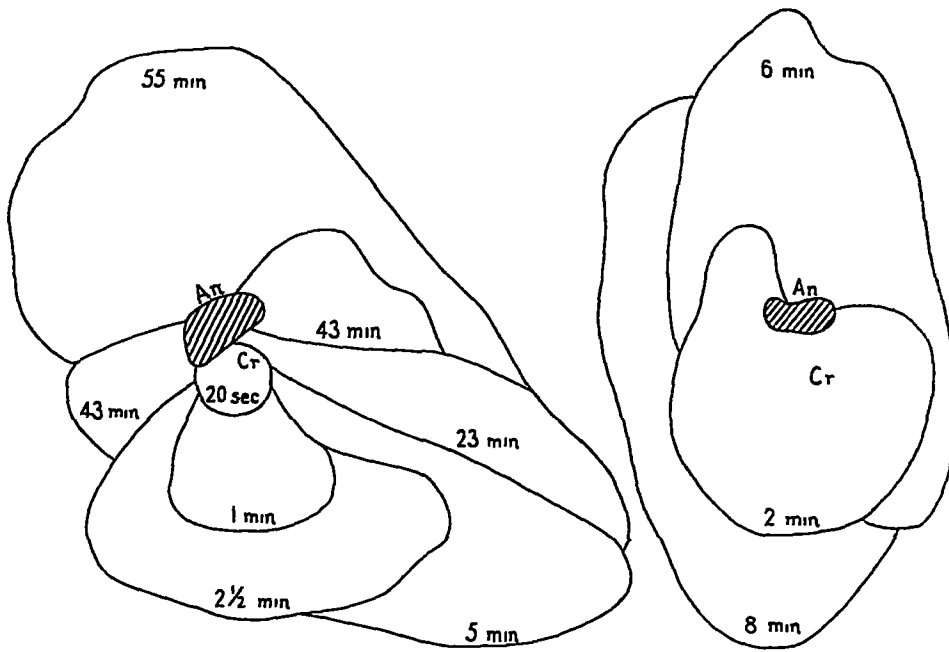


Fig 12

Fig 13

Fig 12 ($\times 2/3$) Crush near anæsthetic barrier T L, July the 18th An area of skin is anæsthetised by intradermal injection of 1% novocaine The area of analgesia is mapped out (An) and it is noted that there is no surrounding hyperalgesia 2 min later

0 min A tiny area of skin (Cr) is now crushed just proximal to the barrier of anæsthetised skin, it causes pain

20 sec The first patch of hyperalgesic skin is defined, it is confined to the proximal side of the barrier and gradually enlarges to fill the contours marked by corresponding times

12 min The injected skin is recovering sensation at its margin

43 min The injected skin has almost fully recovered and as the barrier breaks down, hyperalgesia begins to surround it

55 min The injected skin is normal again, and hyperalgesia has developed fully and surrounds the crush widely in every direction

Fig 13 ($\times 2/3$) Anæsthetic barrier and distant crush A J H, July the 22nd 1% novocaine has been injected to form a short barrier of anæsthetised skin (An) across the arm and after the lapse of several minutes the surrounding skin when tested is found to be normal

0 min A tiny piece of skin (Cr) is now crushed 1 cm away from the barrier

2 min An area of hyperalgesia has developed and is shown in the corresponding outline It extends a little way around, but does not surround, the barrier

6 min Hyperalgesia is now extensive and everywhere widely surrounds the barrier Tested, the barrier is found to be recovering at its margins, but its central part is still fully analgesic

8 min The hyperalgesia has reached its full extent, it remains unchanged after the recovery of the barrier at 15 min

The effector mechanism Of the structure and anatomical connections of the effector nerve endings concerned we have no direct knowledge, but there are indications pointing to what takes place in the skin. In studying the hyperalgesia following injury of the skin, it was concluded (the conclusion was drawn for faradic injury, but is equally applicable to the crush) that, while the distant effect is set up through local nervous channels, its maintenance does not require the continuous flow of these nervous impulses. That they do continue in ordinary circumstances does not here concern us, the point is that their passage soon induces a certain state in the distant skin and that this, once started, develops and continues for long periods of time as a relatively stable affair, being to this extent independent of the original injury. The forms of response to nerve stimulation best known to physiologists are transient, subsiding at once or shortly after the nervous impulses cease to flow, such responses must depend upon reversible or unstable effector processes. The long duration of the reaction here studied strongly suggests that some such process as the release of stable chemical products at the effector endings of the nerves concerned. The hyperalgesia arising from stimulation of the undivided nerve trunk must be regarded as produced similarly, for it is hyperalgesia of the same remarkably stable kind. Moreover, for this nerve trunk stimulation, there is clear evidence that there is no durable change at the point of nerve stimulation, which maintains an influence upon the skin, for nothing develops in skin that is guarded by peripheral nerve block throughout the actual period of nerve stimulation, when that block is released. While thinking about this problem I addressed an enquiry to Professor Foerster of Breslau, asking him if, in his many observations upon stimulation of posterior roots and of cutaneous nerves in man, his patients ever complained of burning pain in the skin. To my great interest he has replied that this occurs from time to time, and he has referred me to an early publication (1) in which he has recorded it. It is to be remembered that his stimulation is not of nerves in continuity but of the distal ends of cut nerves, and thus the pain path from the affected region is broken. Foerster, in speaking of the pain, which nevertheless occurs, records the additional fact that it is abolished by section of the nerve that, overlapping, supplies the same territory. He interprets this to mean that nerve impulses passing to the periphery in one nerve are transferred to the overlapping nerve through some form of common end-apparatus. I think it probable that it is due to a peripheral action of the stimulated nerve on the tissues supplied, liberating substances, and that these act on the pain receptors of the overlapping cutaneous nerve.

The system to which the nerves belong Hyperalgesia such as we are discussing may reasonably be conceived to be the ultimate result of a reduction in the threshold of sensory nerves subserving pain, but such a conception should not be allowed to mislead us into believing that pain nerves form the system through which the local state underlying hyperalgesia is provoked. Consideration will indeed show that the nerves in question

cannot be those concerned with the conveyance of pain impressions from the skin, for these, as is indicated by observations recorded in an appendix, are accurately located by the subject, which could not be the case if the corresponding impulse entered a system of branching axons connecting to a wide area of skin. The idea that hyperalgesia may result from painful impulses referred through a sensory nervous apparatus to a wider peripheral territory would be easier to hold, if such reference was thought to happen in the central nervous system. Such an idea may be fruitful in relation to visceral pain, but a reference in the central nervous system in the case of the diffuse cutaneous hyperalgesia considered here, has already been disproved. The fact is that the cutaneous pain nerves merely register, through sensations which we call hyperalgesia, a state of skin for which they themselves are in no way responsible. But the argument that, because painful cutaneous stimuli can be located by the subject, the pain nerves are not responsible applies also to the nerves subserving touch, and the appreciation of cold and of warmth, for impulses conveying these impressions are all located subjectively, if not with equal, yet with sufficient, precision (see page 413). Thus it seems clear that the sensory nerves can be dismissed. There remains the sympathetic nervous system, a system, incidentally, which is known to provide plexuses or networks of fibres in the skin.

Yet it is to be said at once of the sympathetic nerves that these too are not concerned, for diffuse hyperalgesia is observed in skin completely deprived of them.

This investigation was first carried out upon a patient from whom the right inferior cervical and 2nd dorsal ganglion were excised 7 years ago. Reinvestigated, this patient displays no sign of sympathetic innervation below the right elbow, sweating and goose skin reactions being absent and the vessels of the hand taking no part in general vasomotor reactions. A strong faradic current applied symmetrically to the fronts of the two forearms gave local goose skin on the left but none on the right side, on both sides hyperalgesia developed and spread in the usual way and equally (Fig 14). Similar and equal reactions were obtained on this patient's skin in response to tiny crushes of right and left forearm. Corresponding observations have subsequently been carried out, using the crush as stimulus, upon two other patients presenting unilateral sympathetic nerve degeneration, and have given equally decisive results. Thus we are brought to exclude all the recognised nerves of the skin, first the sensory nerves and now the sympathetic and to consider, in explanation of the phenomena observed, the possibility of a hitherto unrecognised system. That the sensory and sympathetic nerves form the complete cutaneous supply is an idea for which there is no sure foundation. We have come to recognise given systems of nerves by their manifestations, first the sensory nerves because they were found to convey sensory impressions to the brain, and afterwards the vasomotor, pilomotor, and sudorific nerves, as changes in blood supply, erection of hair, and sweating, became recognised as under the governance of separate nerve

systems It will be evident that any system of nerve fibres, which in the exercise of its function gives rise to no obvious and distinctive external manifestations, will tend to escape recognition The fact that the system of nerves, which I conclude to be present, is at present unrecognised is no argument against its existence, the need to postulate a new system of nerves has arisen to explain hitherto unrecognised phenomena The nerves of this system are at present unnamed Because they are associated with local defence against injury I propose to call them the "nocifensor nerves", the defence that I have primarily in mind in justification of this term is the protective hyperalgesia that has here been studied, but I also have in mind the possibility of other protective mechanisms to be described a little later

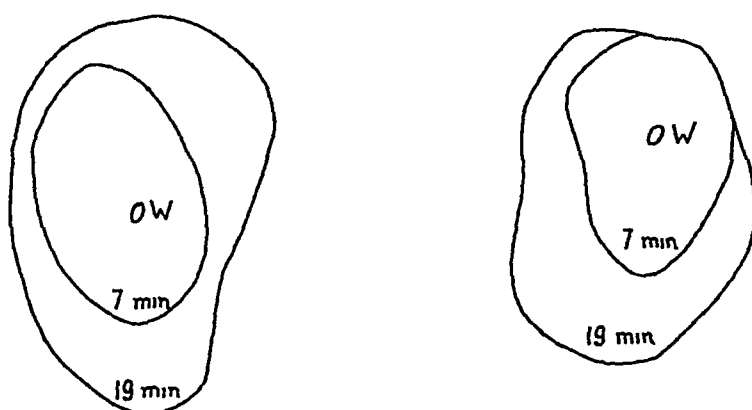


Fig 14 ($\times \frac{3}{2}$) Faradic stimulation and hyperalgesia after sympathectomy Miss H., July the 7th The skin on the front of the lower part of each forearm was faradised for 1 min, with current of usual strength The right arm (right hand diagram) showed no local goose skin, the cervical sympathetic ganglia had been removed on this side several years previously The left arm showed widespread local goose skin during equal stimulation On both sides the skin developed a flare and wheal (W) Surrounding hyperalgesia developed equally on the two arms The areas were mapped out at the 7th and 19th min, in each case, by stroking the skin gently with a blunt point, the blindfold patient responding when hyperalgesic skin was reached

PART V INCIDENTAL OBSERVATIONS AND SPECULATIONS

The main observations and conclusions that it seems desirable to stress are incorporated in Parts I to IV of this paper In proceeding to describe certain incidental observations, and in discussing the relation of the newly discovered system of nerves to other manifestations, some of which have been recorded previously, it is to be understood that we are treading upon less certain ground and that much of what is to be said will be speculative

Relations between widespread hyperalgesia and "erythralgia"

In previous studies of the vascular reactions of the skin to injury in this laboratory, we came to the conclusion that injuries give rise to a common reaction, which we termed the "triple response" and attributed to the release in the skin of "H-substance" from the cells of the skin This triple

response comprises local reddening, local whealing, and a widespread arteriolar "flare" produced through a local nervous mechanism, it is almost always associated with itching of the skin

In more recent observations in conjunction with Hess (6), I have investigated a further and usually a delayed result of cutaneous injury, namely the appearance in the injured skin, generally after the subsidence of whealing, of a curious state, the skin actually injured becomes as we termed it "erythralgic," being deeply reddened and very hyperalgesic. The threshold of the pain nerve endings in this skin is much lowered, friction gives rise to unpleasant burning pain, so does warming the skin to points (40°C or less) that normally are painless, another and remarkable peculiarity is that while friction is immediately and transiently painful, it is followed by a second burning pain after a latent period. Now these facts are important in their relation to the observations discussed in the present paper, and those who desire a full insight into the present work should become familiar with them. According to my experiments with Hess, the hyperalgesic state of erythralgic skin is originally due to the liberation of a pain producing substance from, and into, the skin where this is injured, the substance presumably acting upon and lowering the threshold of the local pain nerve endings. According to these experiments, too, the latent pain following friction results from the release of more pain producing substance. The rapidity with which the erythralgic state follows injury depends, as we showed, upon the kind of injury to which the skin has been submitted, very severe injury may bring it within a few seconds or minutes, milder injuries of the right kind only after hours. According to the kind of injury, the pain producing substance is released rapidly or very slowly from the cells.

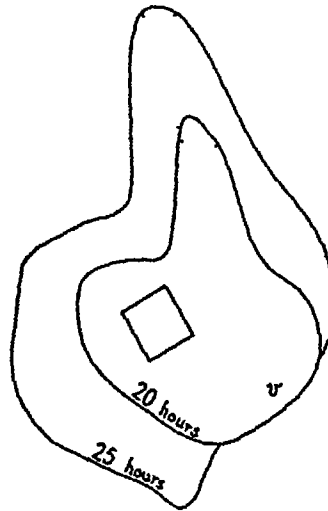
It should not escape notice that in drawing the conclusion that injury can release a pain producing substance from the skin, Hess and I were postulating a substance other than the "H-substance," which is responsible for the reddening and whealing of the more acute stage. There is room for interesting speculation as to what controls the release of different substances that seem to form the basis of different responses.

Enquiry is certain to be fruitful which searches the relationships between the erythralgic condition of skin, which has actually been injured, and the widespread hyperalgesia, which has been discussed in this paper, the following new experiments on freezing emphasise this statement.

In these experiments the skin is frozen in one of two ways, namely, by applying a copper bar at -15°C for 15 or 20 sec, as was done by Lewis and Love (7), or by applying a rod of compressed CO_2 snow for two or three periods of about 5 sec each. Both methods give superficial freezing, but the freeze is harder when CO_2 snow is applied owing to the much lower temperature reached, it is applied repeatedly for short periods to obtain adequate damage without deep penetration.

The milder freezing at -15° is followed by whealing of the skin and itching, the swelling subsides and the skin remains reddened but not

tender (Fig 15 and protocol) In about 20 to 24 hr this same skin swells a little again, smarts a little, and is found to be erythralgic in the full sense already explained The erythralgia lasts for several days and from the time of its development to within a few hours of the time of its disappearance, a surrounding area of skin is slightly but definitely hyperalgesic (as described for faradism on page 377) Thus, there is conspicuous hyperalgesia with



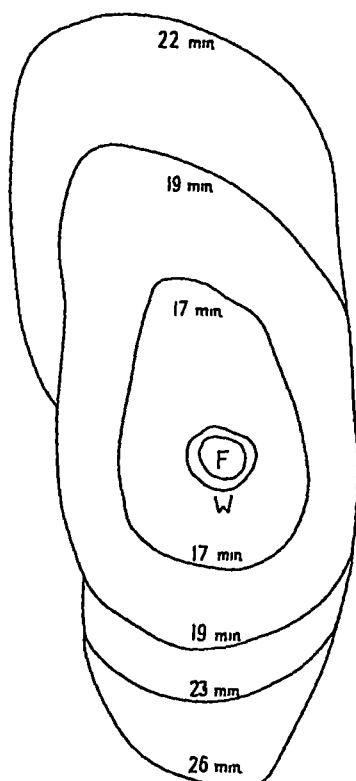
- Fig 15 ($\times \frac{1}{2}$) Hyperalgesia following a freeze T L, May the 13th
- 0 min A square area of skin on the back of right forearm frozen at -15°C for 15 sec
 - $3\frac{1}{2}$ min Itching and whealing has started
 - 8 min Full wheal, itch gone, no hyperalgesia
 - 10 44 min No change No hypersensitivity to copper at 40°C .
 - 6 hr Wheal almost gone No hyperalgesia nor hypersensitivity to heat
 - 18 hr The area frozen and some surrounding skin is tender to touch and the former hypersensitive to heat
 - 20 hr Hyperalgesia more distinct, its area outlined, it runs distally along a large vein *v* (the margins of which are indicated by dotted lines)
 - 25 hr Hyperalgesia fully extended (see outline) Frozen skin very tender, burning when rubbed lightly, and hypersensitive to heat
 - 2 and 3 days Hyperalgesia decreasing Frozen area still sore and hypersensitive to heat
 - 4 days No surrounding hyperalgesia Very slight tenderness of frozen skin, but no detectable hypersensitivity to heat
 - 5 days No hyperalgesia nor hypersensitivity to heat

obvious lowering of the threshold of the pain nerves to warmth in the area of damage, and there is a hyperalgesia of much lower grade, scattered over a wide area of surrounding skin *

If the freeze is the more severe one produced by CO_2 snow (Fig 16 and protocol), then the itching of the initial stages is replaced by smarting or burning, the injured skin becomes erythralgic within about 20 minutes, and

* In Lewis and Hess's paper narrow areas of surrounding tenderness in the erythralgic skin following ultraviolet light burns were ascribed to diffusion or convection of a pain producing substance I am now uncertain whether in the case of ultraviolet light the substance moves into surrounding skin, or whether the surrounding tenderness is produced, as has now been shown in the case of faradism and crushes, through nervous channels

this state lasts from 2 to as much as 6 days, during which it is the rule for the skin to blister * Simultaneously hyperalgesia appears over large areas of surrounding skin and continues as many days as the erythralgia lasts



- Fig 16 ($\times \frac{1}{2}$) Hyperalgesia from freeze A J H, May the 15th upper left forearm
 0, $2\frac{1}{2}$ and 5 min 3 short (5 sec) freezes with CO_2 snow of a circular patch of skin of forearm (F) 14 mm across
 13 min Full whealing (W), extending a little beyond the frozen border, slight burning
 17 min A good deal of local burning felt, area of hyperalgesic skin has recently developed and is outlined
 19 to 26 min Gradual and wide extension of hyperalgesia, the area of whealing has become hypersensitive to copper at 40°
 80 and 160 min Areas of hyperalgesia and central hypersensitivity to heat unchanged
 Slight spontaneous burning
 5 hr Hyperalgesia diminishing in extent Wheal still hypersensitive to copper at 40°
 24 hr Hyperalgesia diminished to the 17 mm outline of yesterday The central area has blistered (11 hr) and is still hypersensitive to 40°
 6 days Hyperalgesia less intense but present, damaged skin still hypersensitive to heat and sore and burning when rubbed
 7 days Soreness and hypersensitivity to heat gone No hyperalgesia in surrounding skin

* Attention has been called previously to the fact that burning pain in the stage of thaw means that the skin will blister

What is here emphasised is that different grades of freezing display a clear relation between the development and maintenance of central erythralgia and of surrounding tenderness. The relationship is not peculiar to freezing but is encountered in the other forms of injury that have been investigated, it is almost certainly an important one. The speculation arising out of it is that the substance locally released by injury may be responsible on the one hand for a local lowering of the threshold of the pain nerve endings by acting directly on these endings, and that it, or possibly some associated substance, may be responsible on the other hand for distant hyperalgesia by an action through the nocifensor nerves.

It may be said, incidentally, that the small area of skin directly damaged by faradism or by crushing, as described earlier, is painfully sensitive to warmth. I use for testing the skin a mass of copper, having flat surfaces of suitable size for application, and kept warm in a bath of water at 40°C. Another example which must now be mentioned is barium chloride. A 0.5% solution of this substance injected intradermally (in doses of 0.02 cc) gives burning pain at the site of injection, coming almost at once. Hyperalgesia develops in the surrounding skin within two or three minutes and about the same time the site of injection is found hypersensitive to warmth. This action of barium chloride* is interesting because the injury may be interpreted as due primarily to precipitation of the sulphates within the cell, thus rapidly upsetting cellular equilibrium. The hypersensitivity to warmth however is in this instance short lasting, while the hyperalgesia of surrounding skin may persist for hours. This forms an additional reason for mentioning barium chloride, the use of which while again illustrating the rapid and simultaneous onset of erythralgia and surrounding hyperalgesia shows that they do not necessarily pass off together. This is probably unimportant, for the minimal concentration of released substance required to produce local erythralgia and distant hyperalgesia through the nerves are not necessarily identical, moreover, as previously shown, distant hyperalgesia persists after the nervous channels leading out from the area of injury are blocked.

Common basis for hyperalgesia

There is a second possible relationship between the diffuse hyperalgesia specially discussed in this paper and the hyperalgesia of the erythralgic state, which Hess and I have described. The idea will obtrude itself that these may be manifestations of states differing from each other merely in degree. It may be stressed that both forms of hyperalgesia have now been ascribed, each on independent evidence, to the release of pain producing substances in the skin. The hyperalgesia is in both cases of the same type, in both some degree of spontaneous pain is often associated, and there is in both a lowering of threshold to pricks, while soreness or actual pain results at once from friction. These resemblances may not be significant in them-

* Calcium and strontium chlorides in 1% solutions give very little effect

selves, but they would become so if it could also be shown that the diffusely hyperalgesic skin displays a second or delayed pain after friction, and has the threshold of its pain responses lowered to heat, for these two qualities have been regarded as peculiar to erythralgic skin. The position is thus Time and again it has been noticed that the skin of diffuse hyperalgesia smarts a little, or that this smarting is brought to light or is increased locally by light friction. When it is brought out in this way it does not follow at once after friction, but after a little period of delay, but it is a very inconspicuous affair compared with the unpleasant pain that similarly follows after rubbing the erythralgic skin. In regard to increased sensitivity to warmth, I have very frequently tested the diffusely hyperalgesic skin by immersing it in water at 40° or by bringing it into contact with copper at this temperature. In most of these observations no definite difference has been detected between the hyperalgesic and the normal skin, but in the more prominent instances of hyperalgesia it has been noticed that warmth is more readily appreciated and its glow is longer felt, although it can rarely be said that actual pain results. The reaction can be interpreted as a borderline reaction. It will be apprehended that neither in the case of the delayed response to friction nor in that of the response to warmth, is the result emphatic, but each permits the interpretation that there is a distinct departure from normality in the apposite direction, and thus brings some support to the general conception that the underlying state in the two instances may be essentially the same, though differing in the degree to which it has progressed. Thus we may conceive that the same pain producing substance is released in the skin, either by direct injury to the skin, or at a distance through special nervous channels. We should add, however, that where the release is supposed to originate through nervous channels rather than from local injury the release must be conceived to be very small in the relative sense.

Finally, there is the possibility that the release of a pain producing substance in the skin, while setting up a state of local hyperalgesia, may reproduce itself at a distance, through the special system of nerves, by causing a similar though much smaller release of substance. In local injury of the skin the release would thus produce conspicuous local hyperalgesia and the release would propagate itself in less degree through the special nerves, manifesting itself in the skin as the milder and diffuse hyperalgesia. Along these lines the curious delay in the appearance of hyperalgesia in the outermost parts of the skin might be explained*. This suggestion—and it is to be emphasised that it is speculative—is not without support.

As has been stated it is thought probable that direct stimulation of the specific nerves causes distal release of pain producing substance. Is it possible that this release can propagate itself in minor degree? When a small nerve, such as a digital nerve, is stimulated it gives rise to hyperalgesia not

* It is not the only explanation that might be put forward, and it could not be used I think to explain more than one transference.

only in its own territory but in the whole cutaneous territory of the ulnar nerve (see page 394), this may conceivably happen in one of two ways. It may be due (1) to direct stimulation of centripetal axons through which the impulses enter centrifugal axons and thus reach the affected skin. Or it may come about (2) through the release of a specific substance in the territory of the stimulated twig, this area now acting as an area of injury, and giving rise to diffuse hyperalgesia in the main nerve territory by the mechanism already discussed. There is a form of experiment which supports the second action as a contributory cause. If the digital nerve to the radial side of the 5th finger is strongly stimulated for 5 minutes through a subcutaneous electrode (see page 390) in the middle of its course, after blocking the same nerve at the base of the finger with a small injection of novocaine, this proximal block of the nerve during the period of stimulation does not prevent the appearance of hyperalgesia in the rest of the skin supplied by the ulnar nerve after the block recovers. Although this observation does not exclude the first action in the ordinary experiment, it does seem to show that a more indirect action, like the second, may be partly responsible.

Related manifestations, general hypothesis of "nocifensor" nerve effects

In the preceding pages evidence has been brought to show that a form of diffuse hyperalgesia can be produced by distal stimulation of a cutaneous nerve trunk, and that an indistinguishable widespread hyperalgesia can be provoked by injuring the skin quite locally, the distant effects being conveyed in the latter instance through a local nervous mechanism having the arrangement of branching axons. When the observations are described in this way a parallel series of facts springs to mind, this series concerns, not hyperalgesia, but vasodilatation.

There is a form of vasodilatation, which has been familiar for many years, it occurs when the distal end of a posterior root or of a cutaneous nerve is stimulated. This action has been termed "antidromic" by physiologists, under the belief that it occurs by reversed conduction through sensory nerves. What alone is proved is that the nerves involved belong to the posterior root system. Nine years ago Marvin and I (8) examined this form of vasodilatation and we found evidence that the nerve stimulation releases vasodilator substance in the skin, H-substance, so we believed, was released from the cutaneous cells. The parallelism between this vasodilatation and the hyperalgesia from cutaneous nerve trunk stimulation, which likewise is here ascribed to released metabolites, is suggestive. It becomes much more suggestive when we note that, while the hyperalgesia of nerve trunk stimulation has its counterpart in nerve trunk vasodilatation, so the hyperalgesia surrounding a local injury has its counterpart in the "flare" of local injury. Let us compare more closely the hyperalgesia and the flare, both of which come to surround the local injury. The hyperalgesia is independent of the sympathetic nervous system, the same has been proved for the flare. Both can occur in skin, the nerves to which are cut off from the

central nervous system, that is to say, both are provoked through a purely local nervous mechanism. The reasons for disbelieving the state of hyperalgesia to be spread through sensory nerves have been given, I now point out, what has previously been overlooked, that a precisely similar argument is applicable to the flare. To explain the spread of the flare from small areas of injury requires arborisations or networks of axons in the skin, which, if subserving sensation, would be incompatible with localisation. When I looked again at the almost forgotten description of the influence of

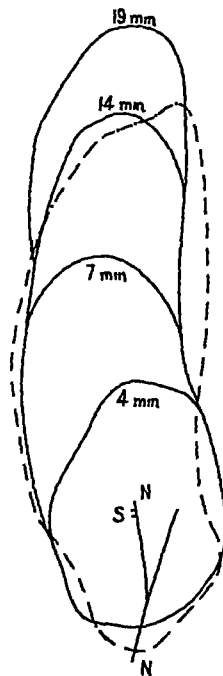


Fig 17 ($\times \frac{1}{2}$) A J H., May the 12th. The anterior branch of the external cutaneous nerve was stimulated at *S* through the skin for 2 min. with a faradic current of usual strength. An area of skin on the forearm became flushed and was mapped out (broken line). Hyperalgesia subsequently developed as indicated by the solid lines and corresponding times from the beginning of stimulation. A repetition of this observation a week later gave a similar result.

anaesthetic barriers in the skin upon the flare, as given by Grant, Marvin and myself (5), after observing the action of similar barriers upon the spread of hyperalgesia (page 398), I was impressed by their remarkable similarity. The conclusion is almost irresistible that the state of hyperalgesia and the flare spreading around a local skin injury, are provoked through one and the same system of nerves and that this system is not sensory, but the separate system here termed "nocifensor."

I have given the main line of argument which links up the two nerve trunk reactions and the two local reactions. There is other evidence.

When a cutaneous nerve trunk is stimulated, an area of hyperalgesia appears over the territory of that nerve. Foerster has shown that these territories are similarly mapped out by cutaneous flushing. In my own experiments this cutaneous flush has often been seen, though owing to the relative weakness of my stimulation—limited as it is by pain—it has never been conspicuous. When the flush appears clearly there is often remarkable correspondence between the mapped area of this flush and the subsequently mapped area of hyperalgesia (*see Fig. 17*). The hyperalgesia surrounding a faradic injury of the skin is in general of less extent than that just considered, so is the corresponding flare. The extent of the flare is in ordinary circumstances largely controlled by the state of capillary tone, but, if the stimulus is put down while the circulation to the skin is arrested, the flare subsequently developed assumes, for reasons not yet clear, a much brighter colour and more circumscribed border. On many occasions I have been forced to remark upon the close correspondence between the borders of such a flare and the borders of full hyperalgesia, correspondence can sometimes be shown to extend to the finer detail of such borders, usually, however, the visible margins of the flare lie within those of hyperalgesia.

Professor Foerster has told me in answer to my direct enquiries that cutaneous nerve trunk stimulation gives rise on occasion to pure itching of the skin, and on other occasions to pain as related on page 400. Small local injuries of the skin are similarly followed by itching or by smarting and soreness. I have now to add a significant fact, recently observed independently by Mr R. Bickford and myself, namely, that the itchy skin, located by light friction, widely surrounds the actual injury, behaving in this and other respects much as does the hyperalgesia which it replaces (Mr Bickford will report his observations separately). This itchy skin is evidently provoked locally through the same system of nerves and serves as an additional link to the several reactions discussed.

To amplify the views already stated is to move farther in the direction of hypothesis. It is improbable that any full view put forward to-day to meet the facts as we recognise them will satisfy the fuller knowledge of the future. The mechanisms with which we are dealing are intricate, and the effects manifold, and much more work will be required to unravel them. But it seems clear that a number of lines are arranging themselves to form what seems to be a single meshwork. It is impracticable to examine here and in adequate detail all the evidence that is relevant to the question, I specially reserve, for I hope future consideration and comparison, the precise nature of the vascular reaction in nerve trunk stimulation and flare. Here especially there remains a difficulty in bringing two reactions, which must be linked, into perfect alignment. The difficulty is that the vasodilatation of nerve trunk stimulation in the cat's paw results, so it has been concluded, from release of H-substance, while the view has also been

expressed that the flare surrounding injury is maintained from the area actually injured, is arteriolar, and is not due to H-substance released in the engorged skin. But the remaining evidence is so weighty that very possibly this seeming discrepancy may disappear when the vascular reactions are further investigated. It has been concluded that a hitherto unrecognised system of nerves exists in the skin and is responsible for diffuse hyperalgesia. The full view which I put forward *as a working hypothesis* is that these nocifensor nerves are responsible for a *number* of reactions, through a release of appropriate substances from and into the skin. They are supposed thus to govern hyperalgesia, itching, and vascular reactions such as arise from and around the local injury. These effects are such as repel injury, guard against renewed injury, and aid local repair. The term "nocifensor" becomes more fully apposite in this wider consideration. Through the nocifensor system, too, such manifestations as may be artificially provoked, vascular flushing ("antidromic") or hyperalgesia, are probably produced, the question as to whether or not such actions as these last ever arise naturally is undecided, though I incline to the view that they can so arise, since Grant, Pearson and Comeau (4) have shown that urticaria may be provoked by central stimulation and by the impulses passing through cutaneous nerves. For this provocation of urticaria implies that, directly or indirectly, cellular substances are released in skin, which release tends to identify the nerves concerned in it with those of the nocifensor system. If this proves to be so, then it will be clear that this system can be set in motion through central nervous action.

Referred tenderness

In discussions on pain and tenderness, the term "referred tenderness" has been used to describe tenderness located by the patient in a region other than that from which it may be supposed to arise. It has been used especially in relation to visceral disease, but not exclusively so. Thus Mackenzie (10) speaks of pain referred from a tooth to other teeth and to the skin of the face. Another notable example in somatic territories is that of pain referred from diaphragm to shoulder.

The present observations obviously throw new light on tenderness arising in skin at a distance from an actual point of skin injury, they explain on similar lines tenderness of facial skin arising from lesions of deeper structure such as the maxillary antrum and the teeth. Thus, they begin to explain manifestations which have been included among instances of "referred tenderness". It cannot yet be said of cutaneous tenderness referred from the viscera that this is produced similarly, it is possible that the mechanism of such reference is distinct. But it is also within the bounds of possibility that the system of nerves, which I have called "nocifensor," is represented in the viscera, and that reflections may happen through this system to the surface of the body. I refer to this possibility to stimulate enquiry and to ensure that it may receive consideration in future investigations that attempt

to unravel the mechanism of tenderness and pain arising out of visceral disease

It seems especially desirable in this connection to refer to the idea of Sturge (13) and of Ross (12), subsequently supported so strongly by Mackenzie, that peripheral irritation may be conveyed to the cord and there diffuse to sensory nerve roots supplying other structures. Sturge and Ross conceived a diffusion from visceral to somatic paths. Mackenzie also accepted diffusion from one somatic path to another within the cord. The observations I have here described, in which the effects of temporarily blocking nerves above or below the point of stimulation are tested, definitely oppose the conclusion that stimulation of skin or of cutaneous nerve leaves an impression on the central nervous system, such as may be referred subsequently as tenderness, they show that when such stimulation gives rise to distant tenderness, it does so, not through the central nervous system, but through a purely peripheral mechanism. Although this demonstration is immediately relevant only to the somatic nerves, it impresses the fact that the ideas of diffusion of impulses and of irritable foci in the cord resulting from visceral disease are purely hypothetical, and renders them less acceptable.

Variable reactions in different individuals

The variability in the effects of faradic stimulation from subject to subject was mentioned early in this paper, the same stimulus may yield large areas of conspicuous hyperalgesia in one subject and little or no hyperalgesia in another. I have not tested large numbers of subjects, but enough to state that hyperalgesia is produced in the majority, though its extent and its degree vary greatly. Sufficient observations have also been made to allow the rule to be stated that if hyperalgesia fails to appear after faradic stimulation of skin and after making little crushes of the skin, it will also fail to appear after the usual stimulation of nerve trunks and nerve branches.

In trying to understand why certain subjects show conspicuous reactions, several possibilities have been considered. One is that if a given subject is used in repeated tests, susceptibility to stimulation may grow. As a main cause of variation this possibility can be excluded. Among the most extensive reactions to faradism found in my own case were the very first reactions of the series, and variations among newly tested subjects have been conspicuous. But there is reason to believe that the power to recognise minor grades of hyperalgesia grows with experience, so that the mapping out of areas becomes more precise and these areas are marked out more extensively by subjects who repeat the tests on themselves day after day. Indeed, one subject who was at first unable definitely to recognise the phenomenon of hyperalgesia to faradic stimulation of his skin, is now able to mark out small surrounding areas with confidence. Such changes of apparent reaction may be accounted for by a cultivated sharpening of sensory

appreciation, combined with a growing understanding of the type and order of changed sensations that are to be observed

But a more fundamental difference in reaction than is thus to be accounted for undoubtedly exists, the difference is not only of degree, sometimes it is of kind. A cutaneous injury, which gives rise to surrounding hyperalgesia in one subject, may give rise to a surrounding area of itchy skin in another, or a given injury may on occasion become surrounded by hyperalgesia bounded by a narrow zone of itchy skin. There is an area of skin on my own arm, which yields hyperalgesia around a single prick through a drop of 1 in 3,000 histamine (1 in 1,000 of acid phosphate in buffered and isotonic solution), while other areas of skin treated in the same fashion always yield an area of itchy skin. In more than one subject an area of itchy skin surrounding a histamine puncture has been noticed to give place after an interval of minutes to a corresponding area of soreness. Slight change in the grade of physical injury of the skin is often enough to determine a change in reaction from itching to burn with hyperalgesia. Foerster, as noted, found the same variation in peripheral nerve stimulations. These facts suggest that variation in the subjective reaction observed by different subjects is mainly due to different degrees of tissue response. Thus the variation might be explained by supposing variation in the release of substances at the effector endings of the nervous mechanism, not only variation in quantity, but in kind, according to the order of increased permeability effected and the sizes of the molecules of substances concerned.

The precise reason for such variations as are noticed must await further elucidation, but the variation in these experiments may have important clinical significance in helping us to understand why referred tenderness is so variable a manifestation of disease.

Appended experiments on cutaneous localisation

Although much seems to have been written about the localisation of sensations derived from the skin, I have discovered few observations relevant to what here concerns us. It is universally recognised that tactile stimuli are localised with great accuracy. In regard to pain, warm and cold sensations, these also are believed to be localised, but care has rarely been taken to exclude the possibility that localisation in these instances is not in fact guided by associated tactile impressions.

Warmth. Blake Pritchard (11), in a critical examination of tactile localisation has contrasted this with warm localisation, using radiant heat as his stimulus and thus avoiding contact with the skin. He finds, for the dorsum of the hands and fingers, that tactile stimuli are localised with an average error of about a $\frac{1}{2}$ cm, and warm stimuli with an average error of about 1 cm.

In a similar endeavour I have used a beam of light concentrated to illuminate a circular spot 4 or 5 mm in diameter on the skin and there developing a temperature of 38° or 39°C as measured in special tests with

thermal junctions The dorsal surfaces of the fingers were tested and the conclusion was reached that blindfold the subject is able to detect the region stimulated as soon as he becomes aware of a distinct sense of warming, with an error of 1 cm or less in the great majority of instances. Curiously, although there is this degree of accuracy, a very occasional mistake is made, in which the stimulus is localised on an adjacent finger though at a correct level.

Cold In testing cold I have used small lead tubes through which water is constantly flowing. Four of these are brought into contact with the skin simultaneously, the area of contact being about 13 by 3 mm. Water at about 34° C is circulated through all and is changed for water at about 24° C in one tube. Laying one of these tubes on each of four fingers, a change to cold in one is invariably and at once localised in the correct finger. The tubes are now laid in parallel series across the dorsum of a chosen finger. If the tubes lie 2 cm apart the change to cold is always localised in the right tube. With the tubes 1 cm apart there are occasional mistakes between adjacent tubes. If two tubes are placed 1½ cm apart on the radial side of a finger and two contacts are placed symmetrically with these on the ulnar side of the same finger, failure promptly to localise the tube that becomes cold is very unusual.

Pain I have used a needle prick as stimulus and have avoided any possibility of guidance from tactile or deep pressure sensations by stopping the circulation to the limb for a suitable period. If the hand is kept in water at 37° C and the circulation to the arm is arrested, all appreciation of simple contacts, light or heavy, is lost in the hand within 25 or 30 min, but needle pricks are still felt (9). The pricks on fingers and hand are localised with an error of less than 1 cm in almost every test, and I have been unable to determine any very appreciable difference in the accuracy of localisation in the normal and in the ischaemic hand.

Comment In the case of each form of sensory stimulation, the tests were carried out upon my own hands and those of A J H, the hands for which the results are especially relevant, since they were the hands chiefly used in the previously recorded experiments on hyperalgesia. The accuracy of localisation was found to be only a little less on the backs of the hands than upon the backs of the fingers, in the case of each form of stimulus tested.

It is clear from these tests that warm, cold, and pain, are all localised with considerable accuracy on the hands, not perhaps with quite the precision of the tactile stimulus, but with sufficient accuracy to show that none of these sensations can be carried through nerve fibres which branch and rebranch to form widely distributed axon systems in the skin.

SUMMARY AND CONCLUSIONS

1 A diffuse and widespread area of hyperalgesia appears in many normal subjects around a point of faradic stimulation or tiny crush of the

skin This hyperalgesia lasts for several or many hours and may be accompanied by a little smarting of the skin

2 Change in the central nervous system is not responsible for this hyperalgesia, which arises out of change in the region of injury and through a local nervous mechanism

3 The impulses travelling through these local nerves set up a process in distant skin of a relatively stable kind, and one which is independent of the original injury

4 Similar hyperalgesia appears around skin damaged in other ways, as by painless freezing, and after the intradermal introduction of very small quantities of skin extracts

5 Similar hyperalgesia may be produced also by stimulating the cutaneous nerve trunks, through the skin or directly by means of a sub-cutaneous electrode The effect is not prevented by previously blocking the nerve proximally, but is prevented by blocking the nerve distally, to the point stimulated Thus this effect is a peripheral one within the territory of the cutaneous nerve's distribution

6 Similar hyperalgesia can be produced in areas of the facial skin by stimulating the mucous membrane of the maxillary antrum, or small dental nerves within the antrum This hyperalgesia involves the whole cutaneous distribution of the maxillary division of the 5th nerve, and reproduces the superficial tenderness that often follows antral catarrh

7 By stimulating a digital nerve, for example that to the radial side of the fifth finger, similar hyperalgesia can be produced in the whole area of skin supplied by the ulnar nerve

8 Diffuse hyperalgesia whether produced by injuring the skin, by stimulating a nerve trunk, or by a small nerve like the digital, is of the same kind, and is produced by one and the same local mechanism

9 Evidence is put forward to show that the nerves concerned are arranged as arborisations of axons in the skin, and that they belong neither to the sensory nor to the sympathetic system The newly discovered system of nerves is named "nocifensor"

SPECULATIONS

10 There are close relations between the hyperalgesia of "erythralgia" and the diffuse hyperalgesia that is here described, and it is thought possible that both may be the result of a release of pain producing substance from the cells of the skin, and that this may occur by direct injury of the skin or as a result of an action through nocifensor nerves The possibility is discussed that local release may stimulate a smaller release at a distance and through nervous channels

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11 The working hypothesis is put forward for examination that the nocifensor nerves are the channels through which are produced, not only diffuse hyperalgesia around an area of injury and hyperalgesia in the territory of a stimulated cutaneous nerve, but also the "flare" that soon surrounds skin injuries, and the vasodilatation in the territory of a stimulated cutaneous nerve or posterior root, which has been termed "antidromic"

12 In this hypothesis the nocifensor nerves are provisionally regarded as influencing the permeability of cells, causing a release of such substance as produce itching and hyperalgesia on the one hand, and vasodilatation on the other

13 The relations of the observations to "referred tenderness" and the significance of variability in the reaction in different individuals, are briefly discussed

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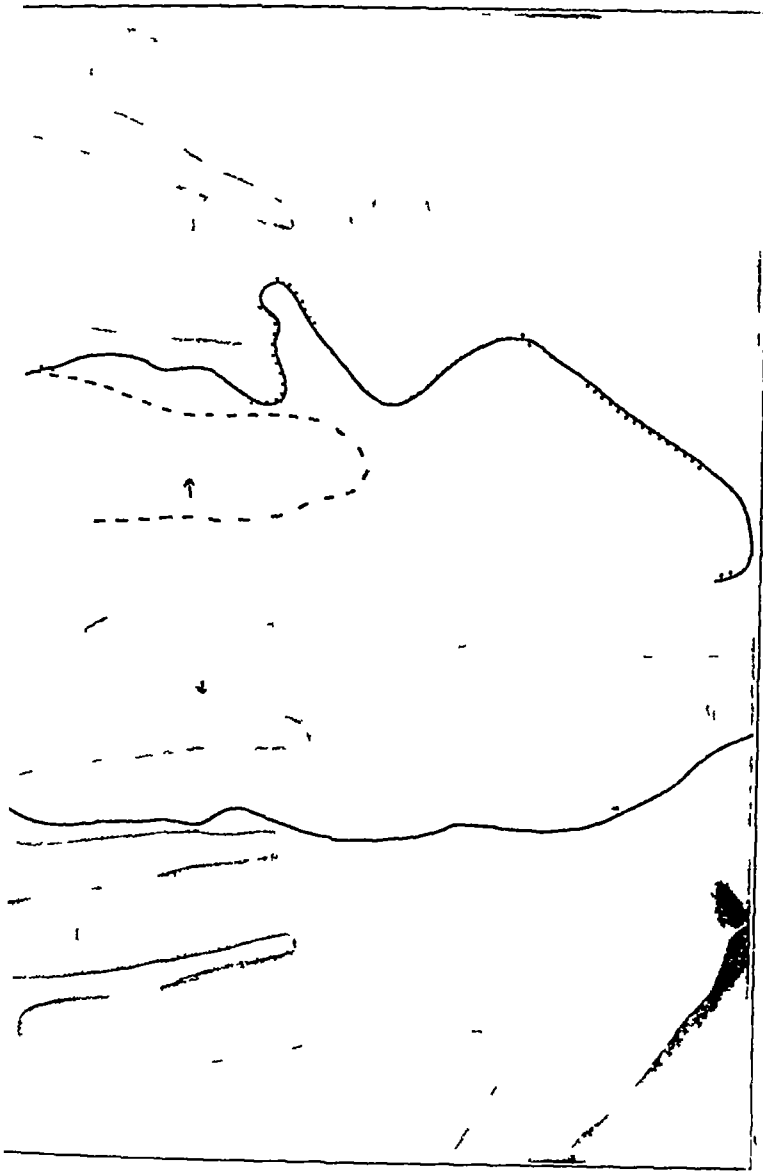


FIG. 18 T. L. Stimulation of digital nerve etc.

May the 15th The digital nerve running on the radial border of the palmar surface of the left little finger (see arrow) was stimulated for 3 min with strong faradic current (coil 60 cm). Very unpleasant fluttering pain running to the tip of finger was felt and when stimulation ceased the finger was a little numb in the territory of the nerve distal to the point stimulated. Hyperalgesia was developing at the 13th minute accompanied by a feeling of distinct burning in fingers 4 and 5. The fully developed area of hyperalgesia which lasted many hours, was mapped out and the hand photographed (broken line).

June the 26th The ulnar nerve was anaesthetised with novocaine and adrenaline at the elbow and the area of anaesthesia and hypoaesthesia mapped out (dotted line). The same point on the little finger (previously marked) was then stimulated with a strong current (coil 55 cm) for 5 min. The current was not felt. About 3 hr later the nerve block recovered and hyperalgesia was found over the area shown by the solid line. It remained until late next day.

The several lines have been incorporated in single photographs of the front and back of the hand.

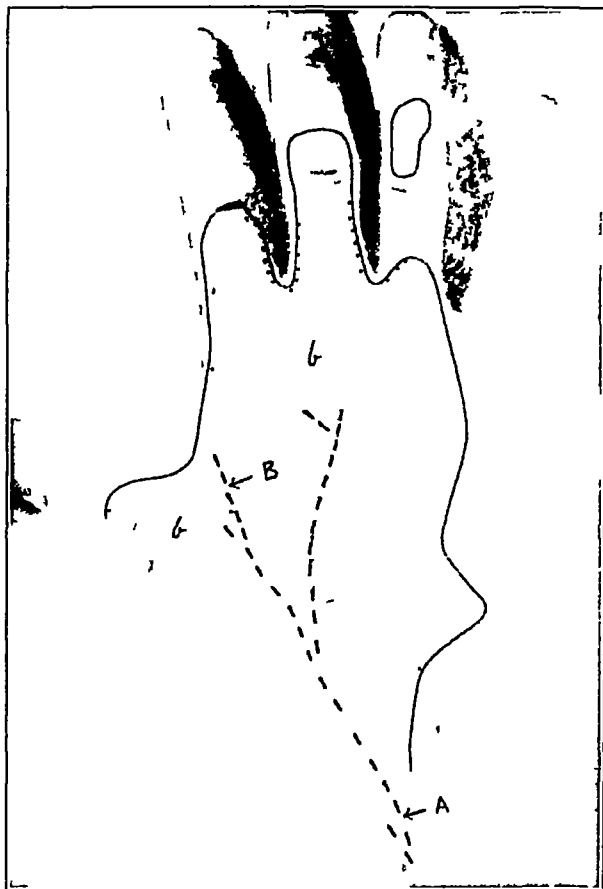


Fig 19 T L Stimulation and anaesthetisation of radial nerve The course of the right radial nerve and its chief branches was traced out with a faradic current and marked indelibly on the skin several days beforehand (heavy broken lines)

June the 16th The main or dorsal part of the nerve was anaesthetised at A and the resultant area of hypoaesthesia very carefully mapped out on a photograph of the hand (the main, outer, dotted line)

June the 10th A small branch of the nerve was stimulated through the skin at B with a strong faradic current for $3\frac{1}{2}$ min Hyperalgesia began to develop 5 min later and was mapped out on the hand when full, without reference to the previous chart This outline of hyperalgesia has been accurately transferred to the present figure (solid line) It is to be said that the isolated area on the ring finger is doubtful slight unexplained hyperalgesia in this region having been noted on a number of subsequent occasions

June the 23rd The branch of the radial nerve stimulated 4 days previously was anaesthetised by a small subcutaneous injection of novocaine at B to display the area bb of hypoaesthesia marking its distribution

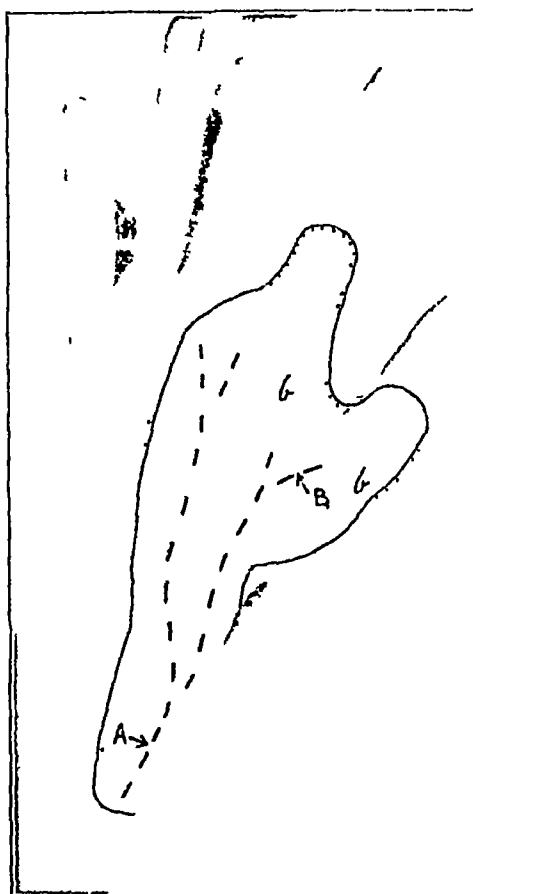


Fig 20 A.J.H. Stimulation and anaesthetisation of radial nerve in another subject. The nerve was traced out and marked indelibly on the skin on June the 16th.

June the 18th A branch of the nerve was stimulated through the skin at *B* for 5 min with a strong faradic current. The fully developed area of subsequent hyperalgesia was charted on a photograph of the hand (solid line).

June the 22nd The nerve was anaesthetised at *A* and the area of hypoaesthesia mapped out (dotted line) without reference to the previous chart.

June the 23rd The branch of the nerve was anaesthetised as nearly as possible at the point *B* of previous stimulation, to display the area *b b* of its distribution.

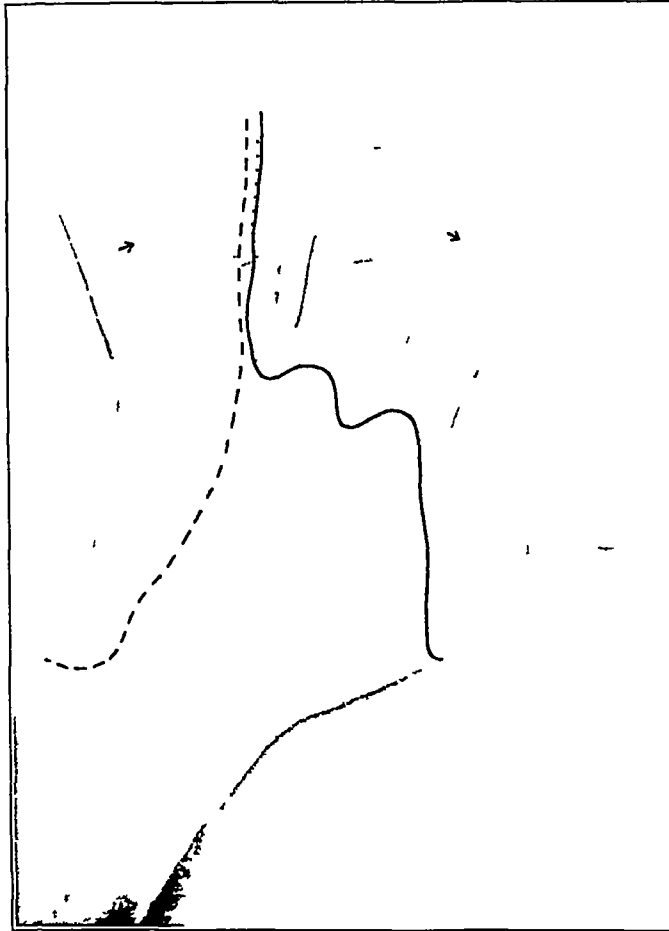


Fig 21 A J H

June the 12th The left ulnar nerve when anaesthetised at elbow gave an area of anaesthesia and hypoaesthesia indicated by the broken line. The previously marked digital nerve to the radial side of the little finger was then stimulated where marked by arrow for 5 min with a strong faradic current which was unfelt. The resultant full area of hyperalgesia was mapped out after recovery of the nerve block (dotted line).

June the 24th The digital nerve to the ulnar side of the index finger was faradised with a strong current for 5 min where indicated by the arrow. The full area of hyperalgesia subsequently developing on the fingers is shown by the solid line.

The subject of this experiment (*see also* Fig 20) is ignorant of the distribution of the main nerves (ulnar median and radial) to the hand.

